COMPETITION FOR VITAMIN B_1 (THIAMIN) STRUCTURES NUMEROUS ECOLOGICAL INTERACTIONS

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ABSTRACT

Thiamin (vitamin B_1) is a cofactor required for essential biochemical reactions in all living organisms, yet free thiamin is scarce in the environment. The diversity of biochemical pathways involved in the acquisition, degradation, and synthesis of thiamin indicates that organisms have evolved numerous ecological strategies for meeting this nutritional requirement. In this review we synthesize information from multiple disciplines to show how the complex biochemistry of thiamin influences ecological outcomes of interactions between organisms in environments ranging from the open ocean and the Australian outback to the gastrointestinal tract of animals. We highlight population and ecosystem responses to the availability or absence of thiamin. These include widespread mortality of fishes, birds, and mammals, as well as the thiamin-dependent regulation of ocean productivity. Overall, we portray thiamin biochemistry as the foundation for molecularly mediated ecological interactions that influence survival and abundance of a vast array of organisms.

INTRODUCTION

ALTHOUGH vitamin B_1 (thiamin) was identified more than a century ago for its importance in maintaining human and domestic animal health, little attention has been paid to this vitamin's potential role in structuring ecological interactions in natural environments. The diversity of approaches used by organisms to produce, degrade, and salvage components of thiamin points to

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strong selection to obtain this vitamin, often at the expense of competitors or hosts. Clues to the ecological importance of thiamin in nature are disparate and have defied ready interpretation for decades, yet we present them here in an attempt to foster a better understanding of an expansive biological topic that is ripe for new insights.

The ecological importance of thiamin has become evident from two different perspectives that point in a common direction: first, studies of domesticated and wild animals that die from thiamin deficiency (Edwin and Jackman 1970; Brown et al. 2005a; Balk et al. 2016) and, second, studies of bacteria and plants that use diverse strategies to produce and acquire thiamin (Bettendorff 2007; Gerdes et al. 2012; Fitzpatrick and Thore 2014; Sañudo-Wilhelmy et al. 2014). Tentative linkages between these perspectives have been proposed for years, but they have not been tied together in a broad ecological context. We begin this review by describing unique features of thiamin biochemistry that are fundamental to its ecological importance. We then review large-scale animal die-offs that initially brought thiamin to the attention of researchers in the 1940s. Throughout this review, we highlight ongoing developments in analytical chemistry and genomics that continue to illuminate the central influence of thiamin in molecularly mediated interactions among diverse organisms.

The Biochemistry of Thiamin in an Ecological Context

Thiamin is a cofactor required for key metabolic pathways in all living things (Jurgenson et al. 2009). Thiamin diphosphate (TDP, also known as thiamin pyrophosphate or TPP) is the active form of this vitamin required for crucial reactions in both anabolic and catabolic intermediary metabolism, including the pentose phosphate pathway and the citric acid cycle (Figure 1). Although the enzymes that bind TDP share little primary sequence similarity except for a few residues that accommodate thiamin and its activation, multiple lines of evidence suggest that the thiamin cofactor was present at the earliest stages of the evolution of life (Frank et al. 2007; Monteverde et al. 2017). Thiamin's long history as an essential organic cofactor underlies the potential for strong selection to evolve numerous ecological outcomes associated with its acquisition and use.

Free thiamin is scarce in the environment and is only available at extremely low (picomolar) concentrations in seawater and freshwater (Table 1). Changes in ambient pH have a substantial effect on thiamin, which degrades at pH > 7 (Maier and Metzler 1957; Windheuser and Higuchi 1962). Under acidic conditions where thiamin is stable, thiamin is a cation with one or two positive charges. This leads thiamin to be adsorbed on clay mineral surfaces by ion exchange with cations under acidic conditions (pH 4–7) that are common in soil (Schmidhalter et al. 1994). We have observed the pH-dependent release of thiamin from a cation exchange matrix in our efforts to concentrate thiamin from ambient water samples using solid phase extraction (in collaboration with K. Edwards, unpublished data), which lends support to two prior studies that examined thiamin availability in natural environments. First, Moore and McLarty (1975) showed that thiamin can be eluted from soil by filtering a slurry of soil and distilled water. More recently, Monteverde et al. (2015) showed that thiamin concentrations in marine sediment porewater were greater than water column concentrations at the same location.

Concentrations of free thiamin within humans and other animals are low due to tight sequestration of the vitamin and the efficient recycling of available thiamin. Typical values found in whole human blood are 70–180 nmol/L TDP (the biologically relevant, active form) and 75–195 nmol/L for total thiamin (thiamin + thiamin monophosphate + thiamin diphosphate; Lu and Frank 2008). Measurements of thiamin concentrations from human tissues or tissues of organisms not consumed by humans are less common in the literature (for exceptions, see Rindi and Ferrari 1977; Tillitt et al. 2005). The scarcity of thiamin measurements from environmental samples and organism tissues largely reflects that analytical methods to measure thiamin are expensive and not amen-

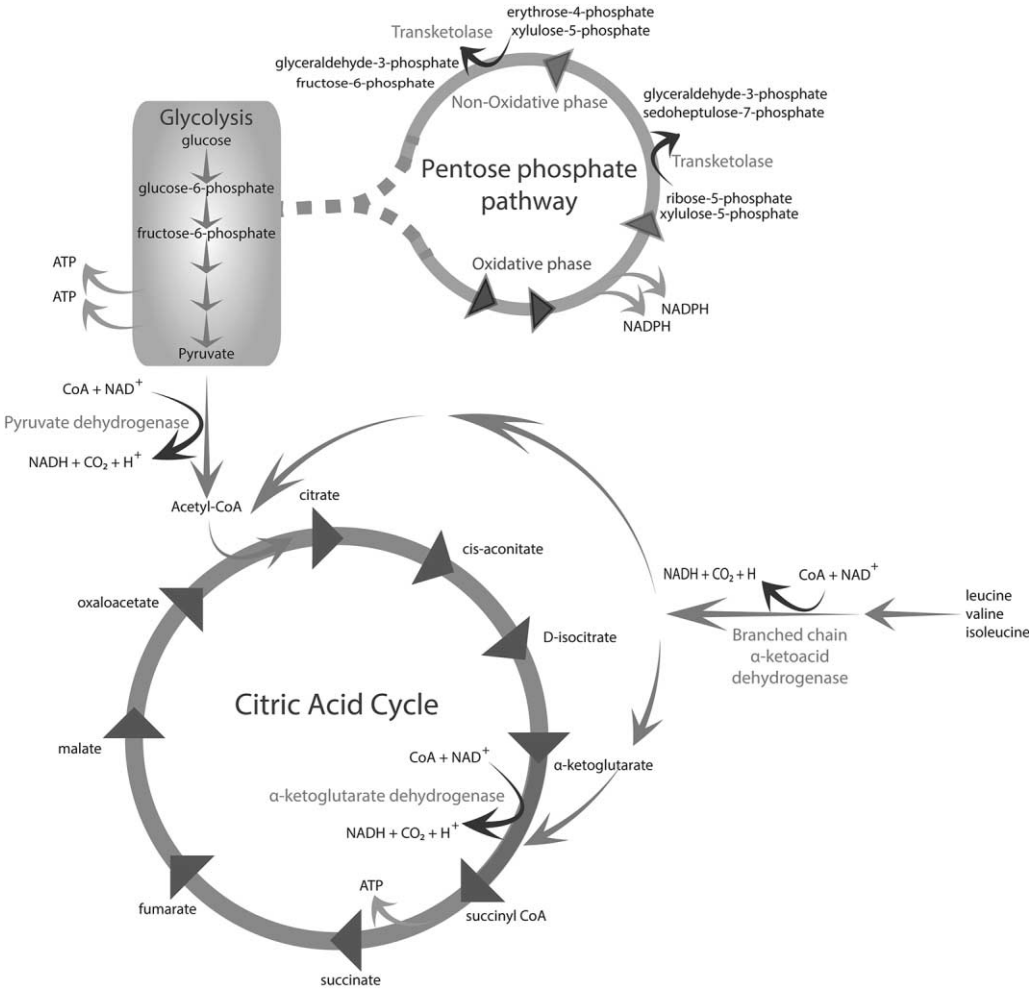

Figure 1. Metabolic Pathways Requiring Thiamin

Thiamin diphosphate (TDP) is a cofactor in several enzymes—including pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase, and branched chain α-ketoacid dehydrogenase—that are associated with glycolysis, the pentose phosphate pathway, and the citric acid cycle. These pathways allow for the production of nicotinamide adenine dinucleotide phosphate (NADPH), adenosine triphosphate (ATP), and ribose-5-phosphate permitting downstream generation of amino acids, nucleic acids, and fatty acids. Thin black arrows highlight enzymatic reactions that require thiamin as a primary cofactor. See the online edition for a color version of this figure.

able to high-throughput analyses (Brown et al. 1998; Okbamichael and Sañudo-Wilhelmy 2005; Edwards et al. 2017).

Many bacteria, fungi, and plants can synthesize thiamin (Fitzpatrick and Thore 2014). The synthesis of thiamin requires independent production of thiazole and pyrimidine precursors that are coupled to form thiamin phosphate as the last step of thiamin synthesis (Jurgenson et al. 2009; Figure 2). This dependence on key intermediates has allowed bacteria and plants lacking a full complement of thiamin synthesis enzymes to develop diverse approaches to obtain TDP, particularly when precursors can be scavenged from the environment (Gerdes et al. 2012; Sañudo-Wilhelmy et al. 2014). These variable approaches indicate that

TABLE 1
Thiamin concentrations reported from environmental samples

Thiamin (pM)	**Location**	**Reference**
	Freshwater	
119-703	Lake Sagami, Japan	Ohwada and Taga (1972)
222-1293	Lake Tsukui, Japan	Ohwada et al. (1972)
15-59	Lake Tahoe, U.S.	Carlucci and Bowes (1972)
12-316	Lake Biwa (main basin), Japan	Kurata and Kadota (1981)
29-797	Lake Biwa (south basin), Japan	Kurata and Kadota (1981)
12-190	Peconic River, New York, U.S.	Gobler et al. (2007)
	Marine	
0-593	Surface waters, Southeast Alaska sea	Natarajan (1968)
330-770	Marine sediment porewater, coastal California, U.S.	Monteverde et al. (2015)
30-280	Marine water column profile, coastal California, U.S.	Sañudo-Wilhelmy et al. (2012)
	Soil	
8900–29,800 nM	Soil water extract	Moore and McLarty (1975)

Additional results from marine waters (with similar concentrations) are presented in Monteverde et al. (2015) and Suffridge et al. (2017).

thiamin synthesis has been shaped by different selection forces from environmental conditions and interactions with other organisms (Helliwell et al. 2013). This contrasts with the relatively invariant approaches used by eukaryotic phytoplankton to produce other B vitamins, such as B_{12}, for which the synthetic pathways seldom differ among taxa (Bertrand and Allen 2012). Helliwell et al. (2013) conclude that dynamic interactions between organisms have shaped divergent approaches for thiamin synthesis often found in closely related taxa. Animals obtain thiamin through consumption of food, with the known exception of ruminants that absorb thiamin released from ruminal microbes as they are lysed during postruminal digestion (Breves et al. 1980, 1981).

The various approaches used by bacteria, plants, and fungi to synthesize thiamin are complex, and this molecule has unique and unexpected properties (Settembre et al. 2003). For example, the biosynthesis of HMP (4-amino-2-methyl-5-hydroxymethylpyrimidine)—the pyrimidine component of thiamin—was described as "without precedent in the biosynthetic or organic chemistry literature" by Lawhorn et al. (2004:2538). Likewise, Fitzpatrick and Thore (2014) reviewed the biochemistry of thiamin synthesis in eukaryotes and highlighted a unique behavior of thiamin synthesis enzymes in fungi and plants, in which they self-destruct and cannibalize cellular cofactors required for other essential biochemical reactions.

The availability and persistence of thiamin is strongly influenced by physical and chemical factors that degrade thiamin, such as ultraviolet radiation, temperature, alkaline conditions, and inorganic bases such as sulfites (Maier and Metzler 1957; Gold et al. 1966; Button 1968; Gold 1968; Boissier and Tillement 1969; Carlucci et al. 1969). Various degradation products of thiamin occur in environmental matrices (Jenkins et al. 2007), and the formation of HMP as a degradation product of thiamin has been reported under varying pH and temperature conditions in laboratory experiments (Windheuser and Higuchi 1962; Boissier and Tillement 1969). Although the degradation products of thiamin in environmental matrices are not thoroughly characterized, it is conceivable that HMP could be formed through similar conditions in environmental waters and soils. Thiamin is also subject

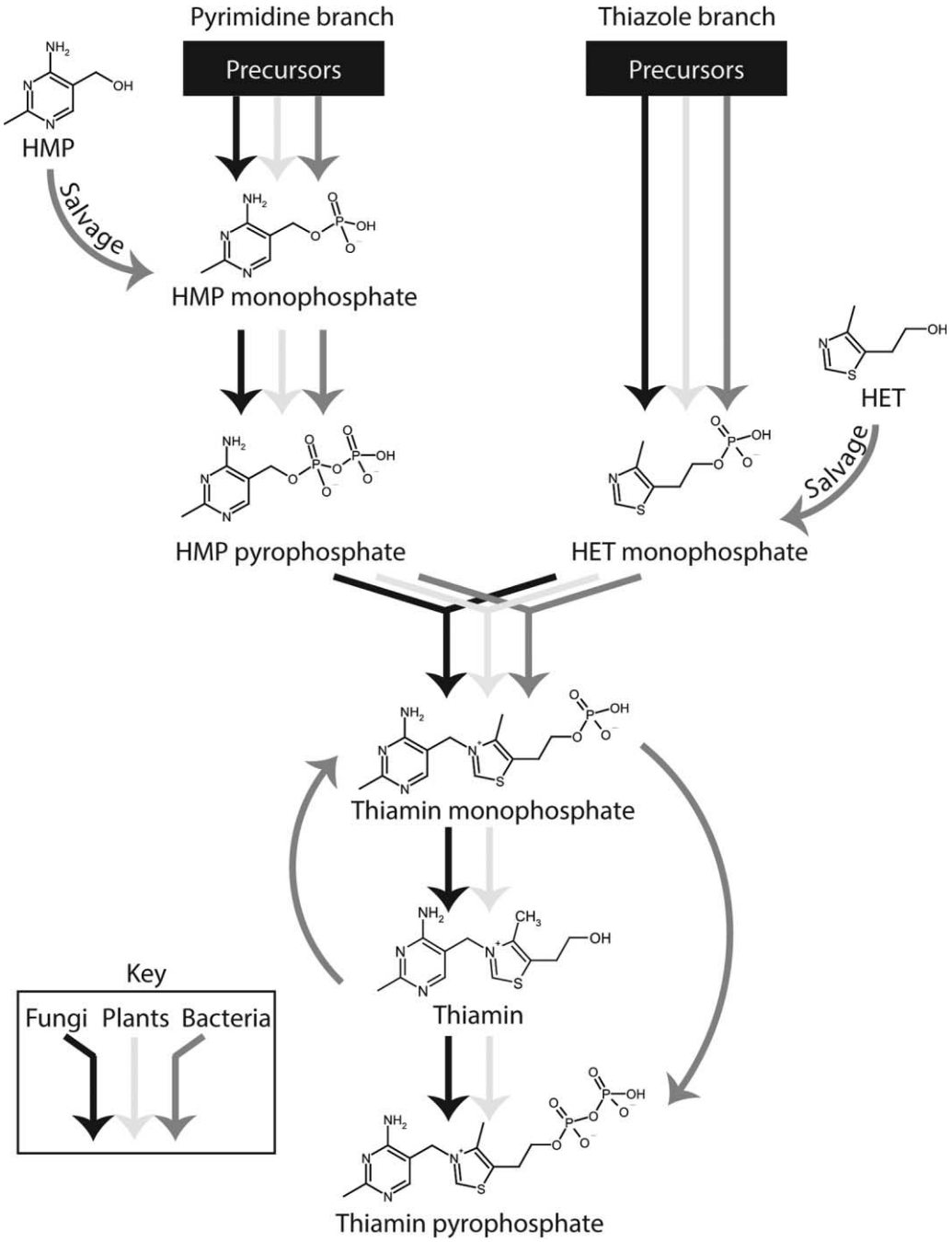

Figure 2. Thiamin Synthesis From Thiazole and Pyrimidine Precursors

Thiamin synthesis by bacteria, plants, and fungi requires independent production or acquisition of a thiazole precursor hydroxyethylthiazole (HET) phosphate and a pyrimidine precursor 4-amino-2-methyl-5-hydroxymethylpyrimidine (HMP) pyrophosphate that combine to form thiamin monophosphate, which is phosphorylated to become the active form of the molecule that serves as the cofactor thiamin pyrophosphate (TDP). See the online edition for a color version of this figure.

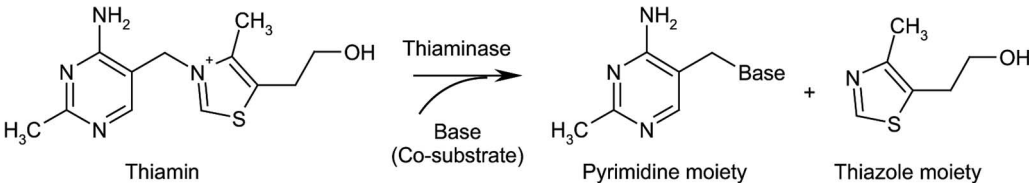

FIGURE 3. THIAMIN IS DEGRADED BY THIAMINASE I AND THIAMINASE II INTO PYRIMIDINE AND THIAZOLE COMPONENTS

to biological degradation, as was first recognized in bacteria producing two distinct thiamin-degrading enzymes (thiaminase I and II) that replace the thiazole moiety of intact thiamin with different nucleophiles (Kimura 1965; Murata 1965; Figure 3).

We suggest that the physical and biological degradation of thiamin has several important consequences for ecological interactions. First, it exacerbates the scarcity of thiamin in natural environments. Second, the degradation of thiamin can increase the availability of its two primary constituents or their analogues; some bacteria, plants, and fungi have enzymes that can salvage these compounds for use in synthesizing thiamin, providing a selectable advantage over those organisms that have to synthesize thiamin from more fundamental components. Third, some degradation products of thiamin are toxic analogues that inhibit enzymatic reactions for which thiamin is a required cofactor (James 1980; Sudarsan et al. 2005).

Because vitamin B_1 is required in small quantities, the import or salvage of components required for thiamin synthesis is a suitable option for thiamin auxotrophs that circumvent implementation of a complete thiamin synthesis pathway (Croft et al. 2006; Zallot et al. 2014). Vitamin auxotrophy is defined as a condition in which organisms require an external source of these essential molecules, but some organisms previously characterized as thiamin auxotrophs are now known to have incomplete synthesis pathways that allow them to make thiamin from precursors such as HMP.

According to the Black Queen Hypothesis presented by Morris et al. (2012), the evolutionary loss of costly genes required to produce thiamin would be expected to occur in circumstances in which an organism could obtain this vitamin or its precursors through other mechanisms. The complexity of phytoplankton and bacterial genomes is beginning to reveal what now appear to be a dazzling array of ecological strategies used by these organisms to obtain essential organic compounds, such as thiamin (Worden et al. 2015). The most thoroughly documented examples of auxotrophy for a thiamin precursor have been shown in microbes that require HMP, the end product of one of the two independent branches of the thiamin biosynthetic pathway (Figure 2); these HMP auxotrophs include the malaria-causing protist *Plasmodium falciparum* and the human pathogen *Listeria monocytogenes* (Wrenger et al. 2006; Schauer et al. 2009). A similar reliance upon acquisition of HMP from the environment has been documented in the abundant SAR11 clade of marine chemoheterotrophic bacteria that cannot use exogenous thiamin and instead are HMP auxotrophs (Carini et al. 2014). These authors observed diel changes in HMP concentrations in open ocean waters and confirmed that several marine bacteria exude HMP in batch culture, indicating that HMP auxotrophs have a ready supply of HMP in marine waters (Carini et al. 2014). Another example of a thiamin salvage pathway targeting HMP was provided in a study showing that enzymes in the TenA protein family are used by soil bacteria (*Bacillus halodurans*) to hydrolyze base-degraded thiamin taken up from the environment, thereby releasing HMP that is subsequently used in thiamin synthesis (Jenkins et al. 2007). TenA enzymes are commonly found in prokaryotes, plants, and fungi, and were originally described as the thiamin-degrading enzyme, thiaminase II (Murata 1965). However, following the description of their role in thia-

min salvage by Jenkins et al. (2007), similar examples have been reported from other organisms (Zallot et al. 2014).

Several early laboratory culture studies also indicated that in the absence of thiamin, phytoplankton can use either the thiazole or pyrimidine moieties from the environment to satisfy a thiamin requirement (Droop 1958; Provasoli and Carlucci 1974). Other studies of bacteria suggested that thiamin degradation products are used in thiamin synthesis (Douthit and Airth 1966; Wang et al. 1968). More recently, studies using genomic techniques have revealed prolific and unrecognized alternatives to the prevailing understanding of thiamin synthesis pathways (Bettendorff 2007; Gerdes et al. 2012; Fitzpatrick and Thore 2014; Sañudo-Wilhelmy et al. 2014). Overall, the complicated chemistry and variety of ecological strategies used by microorganisms to obtain thiamin precursors reflects the presence of conditions that foster competition for thiamin, thiamin precursors, and thiamin degradation products.

The presence of numerous thiamin-sensitive riboswitches in a variety of marine phytoplankton incapable of thiamin synthesis indicates the presence of strong selection pressures to efficiently acquire thiamin and thiamin precursors in ocean environments where thiamin is scarce (McRose et al. 2014). Riboswitches are short sequences within mRNA that regulate translation according to substrate availability. One of the first discovered and the most numerous class of riboswitches is the thiamin pyrophosphate (TPP) riboswitch that regulates thiamin production by shutting down the production of thiamin synthesis enzymes in the presence of TPP (Mironov et al. 2002; Winkler et al. 2002; Breaker 2011). The discovery that riboswitches control numerous thiamin-responsive genes in marine phytoplankton indicates that the presence of thiamin regulates many aspects of primary production in marine ecosystems (McRose et al. 2014; Sañudo-Wilhelmy et al. 2014). Moulin et al. (2013) similarly reported finding numerous thiamin riboswitches in bacteria and plants controlling the synthesis of genes with varied functions. In the freshwater green alga (*Chlamydomonas reinhardtii*), riboswitches independently control synthesis of the pyrimidine and thiazole moieties of thiamin, indicating that synthesis is regulated by the varying availability of these components in the external environment (Moulin et al. 2013). A review of bacteria-diatom interactions indicates that bacteria can sense compounds produced by diatoms, leading to acquisition of diatom-specific products and also opening up the possibility that bacteria can exploit diatoms by causing cell stress or lysis (Amin et al. 2012). Paerl et al. (2015) found that some thiamin auxotrophic marine phytoplankton have unusually high cell quotas of this vitamin, which would make them particularly desirable prey for zooplankton. Sañudo-Wilhelmy et al. (2012) showed that the vertical distributions of B vitamins at different ocean locations were site-specific and independent of each other, suggesting that biological processes (i.e., synthesis, uptake, excretion) were as important as physical processes in determining B vitamin concentrations in ocean waters.

Although it is tempting to draw analogies between processes found in aquatic primary producers and vascular plants in terrestrial environments, the available literature provides few clear insights about thiamin-mediated ecological interactions in land plants. Still, the absence of thiamin synthesis enzymes and the presence of salvage enzymes for the pyrimidine and thiazole moieties of thiamin in the model plants *Arabidopsis* and maize (Gerdes et al. 2012) indicates that land plants may acquire thiamin through complex strategies similar to those found in marine primary producers. In addition, the inconsistent enhancement of horticultural plant growth by thiamin observed in extensive studies in the 1930s and 1940s (Rasmussen 1999) suggests that complex biochemical interactions, not discernible at that time, were responsible for these variable results.

Toxicity and Pathogenecity Associated With Thiamin

An additional interesting and complicating part of the story of the ecological importance of thiamin is its potential for facilitating toxic or pathogenic conditions, which

stems directly from the chemical structure of this vitamin. For example, the production and external release of toxic thiamin antagonists could be used by organisms to overwhelm competitors that are thiamin auxotrophs. Several synthetic thiamin analogues or fragments have been developed that are toxic to microorganisms under laboratory conditions. For example, early laboratory experiments with pyrithiamine, a synthetic analogue of thiamin with substitution of the thiazole ring with a similarly functionalized pyridine ring, demonstrated its toxicity to fungi and bacteria through binding thiamin pyrophosphate riboswitches (Robbins 1941; Woolley and White 1943a,b; Sudarsan et al. 2005). Amprolium, base-substituted thiamin with a methylated pyridine derivative, blocks the transporter responsible for the uptake of thiamin and hence is toxic to certain coccidia protozoa, including *Eimeria* species (James 1980). In natural environments thiamin analogues may be present that have similar toxic effects on competitors and host organisms. The only known naturally produced toxic thiamin analogue is 2′-methoxy-thiamin-pyrophosphate, which is produced by bacteria that convert a pyrimidine analogue called bacimethrin (Nishimura and Tanaka 1963; Reddick et al. 2001). Bacimethrin is produced by a synthetic pathway in the pathogenic bacterium *Clostridium botulinum* (Cooper et al. 2014), although its ecological context has not been explored. The thiamin precursor HMP has also been characterized as toxic to rats (Haughton and King 1958), which is consistent with the observation by Garavito et al. (2015) that in some contexts pyrimidine antimetabolites can disrupt biochemical pathways. Together, the reported toxicity of bacimethrin and HMP support the possibility that organisms produce extracellular thiamin degradation products (e.g., pyrimidine analogues) as a strategy to interfere with thiamin utilization by competitors.

In a review of repair mechanisms used by organisms to eliminate damaged metabolites, Linster et al. (2013) noted that half of the known metabolite repair systems act on highly reactive coenzymes such as thiamin. Another study by this research group identified a Nudix enzyme that renders harmless what they refer to as “damaged” forms of thiamin (Goyer et al. 2013). These authors did not consider the origin of these damaged thiamin analogues, although the production of bacimethrin by a bacterial pathogen suggests that repair or disposal of thiamin analogues could be useful in an ecological context in which thiamin analogues are produced by organisms to enhance their pathogenicity. Overall, the widespread presence of metabolite repair mechanisms supports the idea that toxic byproducts of thiamin and thiamin precursors exert strong natural selection on organisms.

Microbial depletion of externally available thiamin could also foster pathogenicity by competing with hosts for thiamin. This could be similar to interactions described by Schaible and Kaufmann (2004) who observed that pathogenic bacteria often require iron as a growth factor and compete with host organisms for this element. Thiamin is involved in the regulation and activation of immune cells and proteins within the immune system (Manzetti et al. 2014); therefore, the tandem strategy of blocking thiamin-dependent pathways with thiamin analogues and thiamin depletion could enable bacteria to compromise host immune defenses. This might explain the presence of the extracellular thiamin-degrading enzyme known as thiaminase I in the operon that produces bacimethrin, suggesting that these bacteria have a coordinated strategy of removing thiamin from their external environment in host organisms while producing an extracellular toxic thiamin analogue (Cooper et al. 2014).

Further evidence indicating that thiamin removal is associated with pathogenicity is provided by three bacterial groups capable of producing thiaminase I, all of which include closely related pathogenic and nonpathogenic strains (Table 2). This is consistent with the observation by Dethlefsen et al. (2007) that all bacterial pathogens of humans have congeners that are part of the normal microbiota. For example, people living in Southeast Asia develop a disease known

TABLE 2
Confirmed thiaminase I producers and closely related human pathogens containing gene sequences that are nearly identical to thiaminase I

Confirmed thiaminase I producers	Nearly identical sequence similarity in closely related pathogens
Burkholderia thailandensis	*Burkholderia pseudomallei*
Clostridium sporogenes	*Clostridium botulinum*
Naegleria gruberi	*Naegleria fowleri*
Paenibacillus apiarius	
P. thiaminolyticus	
P. dendritiformis	

as melioidosis following infection with the thiaminase I-producing bacterium *Burkholderia pseudomallei*, whereas the closely related *B. thailandensis* does not cause human disease but has been considered a pathogen of insects (Fisher et al. 2012; Pilátová and Dionne 2012). Propst et al. (2010) showed that a Δ*purM* mutant of *B. pseudomallei* rendered incapable of thiamin biosynthesis was avirulent in a mouse model. This is consistent with the hypothesis that *B. pseudomallei* thrives in a thiamin-depleted environment within its host, simultaneously degrading the host immune system while outcompeting bacteria that require thiamin.

A similar pairing of pathogenic and nonpathogenic congeners occurs in the only group of eukaryotes (phylum Percolozoa) known to contain a gene for thiaminase I, the unicellular protozoans *Naegleria fowleri* (pathogenic) and *N. gruberi* (nonpathogenic; Kreinbring et al. 2014). *Clostridium sporogenes* is another thiaminase I-producing bacterium commonly found in sheep and human gastrointestinal tracts that has been generally considered benign, although strains of its close relative *C. botulinum* (also a thiaminase I producer) are pathogenic to many organisms (Hatheway 1990). *Paenibacillus*, another bacterial genus with a thiaminase I considered responsible for Laurentian Great Lakes fish mortality (Honeyfield et al. 2002), also includes many insect pathogens (Gardener 2004), and we have completed experiments with several thiaminase I-containing *Paenibacillus* strains demonstrating that these bacteria are pathogenic to *Drosophila* (unpublished data).

The potential role of thiamin depletion in fostering pathogenicity receives additional support from the observation that most harmful algal bloom (HAB) organisms are vitamin B_1 and B_{12} auxotrophs (Tang et al. 2010). In a review of the biogeochemistry of B vitamins in marine waters, Sañudo-Wilhelmy et al. (2014) provided evidence that B vitamin availability determines phytoplankton species composition and biomass production in some areas of the ocean. These authors also observed that the removal and release of essential B vitamins favors algae that utilize B vitamins released during algal bloom conditions (Sañudo-Wilhelmy et al. 2014). Harmful algal blooms may therefore be produced by organisms capable of using the thiamin released when their toxins kill other organisms.

Animal Mortality From Thiamin Deficiency

The importance of thiamin limitation in nature has been particularly evident in studies from the past 25 years that have shown a substantial influence of thiamin deficiency on mortality in populations of wild animals. For several decades the literature associating thiamin deficiency with animal mortality focused on domesticated animals such as chickens, sheep, cattle, and other ruminant mammals (Shintani 1956; Edwin and Jackman 1970; Thomas et al. 1987; Ramos et al. 2003) rather than free-living organisms in natural environments. This changed in the 1990s when thiamin deficiency was shown to be responsible for the large-scale mortality of fish populations in both the Laurentian Great Lakes and the Baltic Sea (Brown et al. 2005a); it is these observations that prompted our interest in this topic.

Animal mortality from thiamin deficiency was first recognized during the 1940s in mink and foxes raised for fur production (Green and Evans 1940; Stout et al. 1963), after which a similar mortality syndrome was found in free-ranging cattle, sheep, and goats (Edwin and Jackman 1970; Thomas et al. 1987; Ra-

mos et al. 2003). Large die-offs from what can be symptomatically interpreted as thiamin deficiency were also reported from Australian sheep, cattle, goats, and horses as early as 1911 (Henry and Massey 1911), prior to the recognition that vitamin B_1—or any vitamin—was essential to life processes. In fact, animal mortality from thiamin deficiency was the source of insight for understanding the importance of vitamin B_1 as described in a presentation at the 1929 Nobel Prize award ceremony honoring Christiaan Eijkman, who recognized the similarity between beriberi (human thiamin deficiency) and a similar syndrome in chickens.

The extensive literature reporting sheep mortality from thiamin deficiency has focused on the consumption of specific plants as a causal factor for the resulting polioencephalomalacia, primarily focusing upon the presence of thiaminases in these plants and in sheep fecal material (Evans et al. 1975; Linklater et al. 1977; Edwin and Jackman 1981; Candau and Massengo 1982; Thomas 1986; Ramos et al. 2005). Some sheep mortality events have been massive, such as a report by Pritchard et al. (1978) describing the death of 2220 sheep in the Gwydir basin of Australia after grazing upon water ferns (*Marsilea* sp.) that contained thiaminase I (McCleary and Chick 1977). The veterinary literature is replete with examples of sheep mortality from thiamin deficiency, yet this literature has largely focused on the efficacy of thiamin injections to alleviate this problem (e.g., Bourke et al. 2003; Ramos et al. 2005), not the ecological significance of such events.

Thiamin deficiencies in wild populations of predatory fish were first recognized in the 1990s as responsible for a widespread mortality syndrome observed for decades in valuable Baltic Sea and Laurentian Great Lakes fisheries (Fisher et al. 1995). However, the cause of this thiamin deficiency remains unknown. The mortality syndrome was recognized in the 1960s and 1970s by managers of Laurentian Great Lakes fisheries who observed extensive hatchery mortality of newly hatched Pacific salmon raised from eggs collected from wild fish. This was referred to as "early mortality syndrome" (McDonald et al. 1998) at the same time that a similar embryonic mortality syndrome was observed in Baltic Sea hatcheries rearing Atlantic salmon (*Salmo salar*) and sea-run brown trout (*Salmo trutta*; Hansson et al. 2001). In both the Baltic Sea and Laurentian Great Lakes, salmonine fish mortality was regularly observed in recently hatched offspring of wild fish captured in spawning tributaries (McDonald et al. 1998). Twenty years passed before the similarity between these syndromes was recognized and confirmed as resulting from thiamin deficiency (Fisher et al. 1995).

More recent studies have demonstrated that the thiamin deficiency observed in predatory salmonine fishes is caused by the presence of high levels of thiaminase I in their prey (Brown et al. 2005b; Honeyfield et al. 2005a). Yet the source of and conditions responsible for large amounts of thiaminase I in certain fishes remain uncertain. High levels of thiaminase I activity have been routinely observed in clupeid fishes—including alewife (*Alosa pseudoharengus*), gizzard shad (*Dorosoma cepedianum*), and Baltic herring (*Clupea harengus*; Wistbacka et al. 2002; Tillitt et al. 2005)—but mortality from thiamin deficiency has not been reported from these clupeids. Instead, mortality has been observed in early life stages (i.e., shortly after hatching) of predators feeding on these forage fish. For example, sac-fry mortality in Atlantic salmon (Norrgren et al. 1993; Bengtsson et al. 1999) and sea-run brown trout (Landergren et al. 1999) in the Baltic Sea has been linked to consumption of clupeid prey containing thiaminase I. A similar type of mortality in sac fry of North American lake trout has been documented (Honeyfield et al. 2005b). Fish hatchery managers have developed a practice similar to that used by veterinarians to address sheep mortality: by adding thiamin to hatchery water systems, they increase thiamin levels in salmonine eggs that otherwise exhibit thiamin deficiency and thereby eliminate sac-fry mortality (Koski et al. 1999; Wooster et al. 2000; Brown et al. 2005a).

Additional studies have documented thiamin deficiency as a cause of mortality in

nondomesticated animals consuming fish prey with high thiaminase I levels, such as wild alligators (Honeyfield et al. 2008) and captive marine mammals. Thiamin deficiency in marine mammals was first reported for a captive gray seal (*Halichoerus grypus*) fed smelt (*Osmerus mordax*; Myers 1955). This was followed by reports of thiamin deficiency in captive California sea lions (*Zalophus californianus*; Rigdon and Drager 1955) and bottlenosed dolphin (*Tursiops truncatus*) maintained on fish diet (White 1970) and captive harbor seals fed a diet including Baltic herring (a clupeid fish) and smelt (Wohlsein et al. 2003). More recently, mortality from thiamin deficiency was reported in captive harbor seals fed fish with high levels of thiaminase I (Croft et al. 2013).

Bird mortality from thiamin deficiency has been reported from captive herring gulls fed an exclusive diet of alewife from Lake Michigan (Friend and Trainer 1969). Bartoli et al. (1997) also reported that young yellow-legged gulls raised from eggs in captivity died within one week of hatching when fed an exclusive diet of unspecified fish. Balk et al. (2009) described thiamin deficiency as the cause of large-scale declines of three abundant European bird species living near the Baltic Sea (herring gulls, starlings, and common eider). Although these authors did not link this mortality to fish consumption by their study bird populations, this and other work by this research group (Balk et al. 2016) has expanded recognition of the potential large-scale ecological influence of thiamin deficiency upon a broader range of wild animal populations.

Balk et al. (2009) have provided the best evidence that mortality of wild animal populations from thiamin deficiency had increased through time. By contrast, fisheries mortality associated with thiamin deficiency was recognized almost simultaneously in the 1960s and 1970s by managers of Laurentian Great Lakes and Baltic Sea fisheries, but earlier problems of this nature could have gone unnoticed. A unique, 30-year record of coho salmon mortality in a Michigan hatchery shows a variable and vaguely increasing trend, but this trend was not suitable for statistical analysis (Brown et al. 2005a). The question of whether wild animal mortality from thiamin deficiency has increased in recent decades therefore likely remains unanswerable unless future research identifies anthropogenic causes that have contributed to increased mortality.

Human Thiamin Deficiency From Consuming Wild Organisms

Human morbidity resulting from thiamin deficiency in the 19th century prompted subsequent research showing that changes in prevailing diets and food processing exacerbated thiamin deficiency, which was then largely alleviated by enriching human food sources with added thiamin (Williams 1961). Vitamin B deficiencies were first recognized in humans relying upon diets with little available thiamin, but studies of human microbial endosymbionts also provided the first clues that biochemical changes in the gastrointestinal tract might lead to thiamin deficiency and death. These clues were developed in a remarkable series of studies by the Vitamin B Research Committee of Japan that occurred at the end of World War II when that nation's population faced devastating food shortages (Shimazono and Katsura 1965). Prior to the war, Japan had made substantial progress in addressing widespread human B vitamin deficiencies associated with the prevailing diet of polished rice. Within a decade after the war's end, this committee's studies helped eliminate this human health problem in Japan, while at the same time providing fundamental insights for understanding thiamin deficiency as an ecological and environmental concern.

The Japanese literature on beriberi and thiamin was reviewed and summarized in an English translation published in the mid-1960s (Shimazono and Katsura 1965) that described the presence of thiamin-degrading bacteria in feces from a substantial proportion (5–18%) of Japanese residents (Murata 1965). Human consumption of organisms containing thiaminase I, such as raw seafood, had been previously and speculatively described as a potential causal factor of thia-

min deficiency in Asian countries (Williams 1961), but the origin of thiamin-degrading enzymes was unknown. The ill-fated explorers Robert Burke and William Wills, who died on their return trip after traversing the Australian continent in 1860, provide a frequently cited example of human thiamin deficiency caused by the consumption of food containing thiaminase I. The diaries of Burke and Wills have led historians to conclude that they died from thiamin deficiency caused by consuming raw waterfern, *Marsilea drummondii*, known as nardoo (Earl and McCleary 1994). Although this plant contains high levels of thiaminase I (McCleary and Chick 1977), it was commonly consumed by aboriginal hunter-gatherers, who cooked the plant—and therefore denatured the thiamin-degrading enzyme—before eating it. Additional examples of human thiamin deficiency caused by the consumption of plants with thiaminase I have been reported, such as an experimental study in which human subjects consumed bracken fern, another plant with high thiaminase I levels (Samruatruamphol and Parsons 1955).

Studies of human thiamin deficiency in West Africa have identified insects as containing thiamin-degrading enzymes that produce dizziness, vomiting, and ataxia when consumed in large quantities (McCandless 2010). As with other examples of thiaminase I-induced thiamin deficiency, this syndrome was first described as a neurological disease referred to as "encephalitis tremens" without any knowledge of its underlying etiology or connection to thiamin deficiency (Wright and Morley 1958). Subsequent studies in western Nigeria concluded that this human thiamin deficiency syndrome was caused by consumption of larvae of the lepidopteran *Anaphe venata* (Adamolekun et al. 1997), after which Nishimune et al. (2000) confirmed that these larvae contained high levels of thiaminase I.

Unfortunately, outbreaks of human mortality from thiamin deficiency continue to occur in individuals consuming adequate dietary sources of thiamin, such as a 2014 event on a Pacific island (Nilles et al., unpublished manuscript). Similarities between this human mortality and mortality from thiamin deficiency in other animal populations support the idea that unspecified ecological interactions—perhaps between hosts and endosymbionts or involving pathogenic organisms—are responsible for these events.

Thiamin-Mediated Ecological Interactions

A central tenet of ecological theory is that organisms compete for nutrients and that this competition affects many aspects of plant communities, such as species diversity and relative abundance (Tilman 1988). Empirical studies exploring competition for chemical resources have traditionally focused on the outcomes of competition for nitrogen and phosphorus, with less attention paid to other nutrients such as potassium and silica (Miller et al. 2005). Despite an awareness that more complicated molecules might be subject to competition among organisms, most ecological studies of nutrient limitation have focused on the sequestration, degradation, and transformation of relatively simple molecules containing nitrogen (e.g., N_2, NO_3, and NH_4). However, it is logical to expect that the requirement for other more complicated chemical compounds, such as thiamin, would constitute a strong selection force and would induce organisms to develop the capacity to use these resources in a manner that renders them unavailable to competitors.

In the previous sections we have provided examples suggesting that organisms use many different strategies to acquire thiamin and can use thiamin degradation products in a manner that gives them a competitive advantage over other organisms living in the same environment. Most of these examples were microbial or have a plausible microbial connection. For example, one of the mysteries associated with the thiamin-degrading enzyme, thiaminase I, is whether its presence in animals is due to de novo production by these organisms or by microbial endosymbionts (Richter et al. 2012). The localized distribution of this enzyme in the rhizomes of bracken fern and gastrointestinal tract of

fishes is consistent with the hypothesis that microbial sources are responsible for the presence of thiaminase I in these organisms (Kraft et al. 2014). Regardless of whether thiaminase I is produced de novo or by microbial endosymbionts, biochemical transformations of thiamin almost certainly influence interspecies interactions, biological community composition, and broad-scale ecosystem processes such as the production of phytoplankton in ocean environments.

Conclusion

Abundant evidence suggests that the acquisition and degradation of thiamin plays a central role in competitive interactions, symbiotic associations, and pathogenic interactions that have large-scale influences upon animal mortality and marine productivity. It has been obvious for more than a century that organisms need to produce or consume enough thiamin to survive. But it has not been obvious that the unique biochemistry of this vitamin places it as the focus of an extensive set of ecological interactions.

In considering the ecological influence of biochemical transformations of thiamin, it is important to consider the potential for anthropogenic alterations of biochemical cycles involving thiamin synthesis and degradation. Specifically, thiamin has been increasingly added to the human and animal food supply since the chemical synthesis of this vitamin was developed in the 1930s (Williams 1961). Industrial production of thiamin was approximately 3300 tons in the 1990s (Burdick 1998), and most of the thiamin sold worldwide is used for dietary supplements. Although this practice has unquestionably contributed to improvements in human health, its potential environmental consequences have never been considered. We suggest that human activities have provided concentrated sources of thiamin at such locations as sewage treatment plants and animal feedlots, based on the observation that excess thiamin cannot be stored by humans and is excreted (Tasevska et al. 2008). Physical and biological degradation would then lead to the presence of atypically large concentrations of thiamin degradation products (e.g., HMP) suitable for the proliferation of organisms associated with harmful algal blooms and other pathogenic conditions.

In this review we suggest that an ecological battle is being fought in diverse ecosystems over thiamin and its pyrimidine and thiazole precursors. Competition for thiamin occurs among organisms living in the same environment, as well as among organisms living within other organisms, leading to pathogenicity. This ecological competition occurs in open ocean waters of the Sargasso Sea, one of the most nutrient poor ecosystems on Earth, and this competition occurs within the nutrient rich gastrointestinal tracts of fish in the Laurentian Great Lakes and sheep grazing in Australia. Casualties from this competition have been evident for decades in mass mortality events observed in fishes and ruminant mammals but, until now, no effort has been made to develop a broad ecological framework for understanding these phenomena.

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REFERENCES

Adamolekun B., McCandless D. W., Butterworth R. F. 1997. Epidemic of seasonal ataxia in Nigeria following ingestion of the African silkworm *Anaphe venata*: role of thiamine deficiency? *Metabolic Brain Disease* 12:251–258.

Amin S. A., Parker M. S., Armbrust E. V. 2012. Interactions between diatoms and bacteria. *Microbiology and Molecular Biology Reviews* 76:667–684.

Balk L., Hägerroth P.-Å., Åkerman G., Hanson M., Tjärnlund U., Hansson T., Hallgrimsson G. T.,

Zebühr Y., Broman D., Mörner T., Sundberg H. 2009. Wild birds of declining European species are dying from a thiamine deficiency syndrome. *Proceedings of the National Academy of Sciences of the United States of America* 106:12001–12006.

Balk L., Hägerroth P.-Å., Gustavsson H., et al. 2016. Widespread episodic thiamine deficiency in Northern Hemisphere wildlife. *Scientific Reports* 6:38821.

Bartoli P., Bourgeay-Causse M., Combes C. 1997. Parasite transmission via a vitamin supplement. *BioScience* 47:251–253.

Bengtsson B.-E., Hill C., Bergman Å., Brandt I., Johansson N., Magnhagen C., Södergren A., Thulin J. 1999. Reproductive disturbances in Baltic fish: a synopsis of the FiRe project. *Ambio* 28:2–8.

Bertrand E. M., Allen A. E. 2012. Influence of vitamin B auxotrophy on nitrogen metabolism in eukaryotic phytoplankton. *Frontiers in Microbiology* 3:375.

Bettendorff L. 2007. At the crossroad of thiamine degradation and biosynthesis. *Nature Chemical Biology* 3: 454–455.

Boissier J. R., Tillement J. P. 1969. Study of the stabilization by histidine of the thiamine in aqueous solution at 37 degrees C. *Annales Pharmaceutiques Francaises* 27:743–748.

Bourke C. A., Rendell D., Colegate S. M. 2003. Efficacy of the prophylactic use of thiamine and pyridoxine in sheep during an outbreak of *Phalaris aquatica* "Polioencephalo-malacia-like sudden death" poisoning. *Australian Veterinary Journal* 81:637–638.

Breaker R. R. 2011. Prospects for riboswitch discovery and analysis. *Molecular Cell* 43:867–879.

Breves G., Hoeller H., Harmeyer J., Martens H. 1980. Thiamin balance in the gastrointestinal tract of sheep. *Journal of Animal Science* 51:1177–1181.

Breves G., Brandt M., Hoeller H., Rohr K. 1981. Flow of thiamin to the duodenum in dairy cows fed different rations. *Journal of Agricultural Science* 96:587–591.

Brown S. B., Honeyfeld D. C., Vandenbyllaardt L. 1998. Thiamine analyses in fish tissues. *American Fisheries Society Symposium* 21:73–91.

Brown S. B., Fitzsimons J. D., Honeyfield D. C., Tillitt D. E. 2005a. Implications of thiamine deficiency in Great Lakes salmonines. *Journal of Aquatic Animal Health* 17:113–124.

Brown S. B., Brown L. R., Brown M., Moore K., Villella M., Fitzsimons J. D., Williston B., Honeyfield D. C., Hinterkopf J. P., Tillitt D. E., Zajicek J. L., Wolgamood M. 2005b. Effectiveness of egg immersion in aqueous solutions of thiamine and thiamin analogs for reducing early mortality syndrome. *Journal of Aquatic Animal Health* 17:106–112.

Burdick D. 1998. Thiamine. Pages 152–171 in *Kirk-Othmer Encyclopedia of Chemical Technology*, edited by R. E. Kirk. New York: Wiley.

Button D. K. 1968. Selective thiamine removal from culture media by ultraviolet irradiation. *Applied Microbiology* 16:530–531.

Candau M., Massengo J. 1982. Evidence of a thiamine deficiency in sheep fed maize silage. *Annales de Recherches Veterinaires* 13:329–340.

Carini P., Campbell E. O., Morré J., Sañudo-Wilhelmy S. A., Thrash J. C., Bennett S. E., Temperton B., Begley T., Giovannoni S. J. 2014. Discovery of a SAR11 growth requirement for thiamin's pyrimidine precursor and its distribution in the Sargasso Sea. *ISME Journal* 8:1727–1738.

Carlucci A. F., Bowes P. M. 1972. Determination of vitamin B_{12}, thiamine, and biotin in Lake Tahoe waters using modified marine bioassay techniques. *Limnology and Oceanography* 17:774–777.

Carlucci A. F., Silbernagel S. B., McNally P. M. 1969. Influence of temperature and solar radiation on persistence of vitamin B_{12}, thiamine and biotin in seawater. *Journal of Phycology* 5:302–305.

Cooper L. E., O'Leary S. E., Begley T. P. 2014. Biosynthesis of a thiamin antivitamin in *Clostridium botulinum*. *Biochemistry* 53:2215–2217.

Croft L., Napoli E., Hung C. K., St. Leger J., Gearhart S., Heym K., Wong S., Sakaguchi D., Lin A., Puschner B., Giulivi C. 2013. Clinical evaluation and biochemical analyses of thiamine deficiency in Pacific harbor seals (*Phoca vitulina*) maintained at a zoological facility. *Journal of the American Veterinary Medical Association* 243:1179–1189.

Croft M. T., Warren M. J., Smith A. G. 2006. Algae need their vitamins. *Eukaryotic Cell* 5:1175–1183.

Dethlefsen L., McFall-Ngai M., Relman D. A. 2007. An ecological and evolutionary perspective on human–microbe mutualism and disease. *Nature* 449:811–818.

Douthit H. A., Airth R. L. 1966. Thiaminase I of *Bacillus thiaminolyticus*. *Archives of Biochemistry and Biophysics* 113:331–337.

Droop M. R. 1958. Requirement for thiamine among some marine and supra-littoral protista. *Journal of the Marine Biological Association of the United Kingdom* 37:323–329.

Earl J. W., McCleary B. V. 1994. Mystery of the poisoned expedition. *Nature* 368:683–684.

Edwards K. A., Tu-Maung N., Cheng K., Wang B., Baeumner A. J., Kraft C. E. 2017. Thiamine assays—advances, challenges, and caveats. *ChemistryOpen* 6:178–191.

Edwin E. E., Jackman R. 1970. Thiaminase I in the development of cerebrocortical necrosis in sheep and cattle. *Nature* 228:772–774.

Edwin E. E., Jackman R. 1981. Ruminant thiamine requirement in perspective. *Veterinary Research Communications* 5:237–250.

Evans W. C., Evans I. A., Humphreys D. J., Lewin B., Davies W. E. J., Axford R. F. E. 1975. Induction

of thiamine deficiency in sheep, with lesions similar to those of cerebrocortical necrosis. *Journal of Comparative Pathology* 85:253–267.

Fisher J. P., Spitzbergen J. M., Iomonte T., Little E. E., Delonay A. 1995. Pathological and behavioral manifestations of the "Cayuga Syndrome," a thiamine deficiency in larval landlocked Atlantic salmon. *Journal of Aquatic Animal Health* 7:269–283.

Fisher N. A., Ribot W. J., Applefeld W., DeShazer D. 2012. The Madagascar hissing cockroach as a novel surrogate host for *Burkholderia pseudomallei*, *B. mallei* and *B. thailandensis*. *BMC Microbiology* 12:117.

Fitzpatrick T. B., Thore S. 2014. Complex behavior: from cannibalism to suicide in the vitamin B_1 biosynthesis world. *Current Opinion in Structural Biology* 29:34–43.

Frank R. A. W., Leeper F. J., Luisi B. F. 2007. Structure, mechanism and catalytic duality of thiamine-dependent enzymes. *Cellular and Molecular Life Sciences* 64: 892.

Friend M., Trainer D. O. 1969. Aspergillosis in captive herring gulls. *Bulletin of the Wildlife Disease Association* 5:271–275.

Garavito M. F., Narváez-Ortiz H. Y., Zimmermann B. H. 2015. Pyrimidine metabolism: dynamic and versatile pathways in pathogens and cellular development. *Journal of Genetics and Genomics* 42:195–205.

Gardener B. B. M. 2004. Ecology of *Bacillus* and *Paenibacillus* spp. in agricultural systems. *Phytopathology* 94:1252–1258.

Gerdes S., Lerma-Ortiz C., Frelin O., Seaver S. M. D., Henry C. S., de Crécy-Lagard V., Hanson A. D. 2012. Plant B vitamin pathways and their compartmentation: a guide for the perplexed. *Journal of Experimental Botany* 63:5379–5395.

Gobler C. J., Norman C., Panzeca C., Taylor G. T., Sañudo-Wilhelmy S. A. 2007. Effect of B-vitamins (B_1, B_{12}) and inorganic nutrients on algal bloom dynamics in a coastal ecosystem. *Aquatic Microbial Ecology* 49:181–194.

Gold K. 1968. Some factors affecting the stability of thiamine. *Limnology and Oceanography* 13:185–188.

Gold K., Roels O. A., Bank H. 1966. Temperature dependent destruction of thiamine in seawater. *Limnology and Oceanography* 11:410–413.

Goyer A., Hasnain G., Frelin O., Ralat M. A., Gregory J. F. III, Hanson A. D. 2013. A cross-kingdom Nudix enzyme that pre-empts damage in thiamin metabolism. *Biochemical Journal* 454:533–542.

Green R. G., Evans C. A. 1940. A deficiency disease of foxes. *Science* 92:154–155.

Hansson S., Karlsson L., Ikonen E., Christensen O., Mitans A., Uzars D., Petersson E., Ragnarsson B. 2001. Stomach analyses of Baltic salmon from 1959–1962 and 1994–1997: possible relations between diet and yolk-sac-fry mortality (M74). *Journal of Fish Biology* 58:1730–1745.

Hatheway C. L. 1990. Toxigenic clostridia. *Clinical Microbiology Reviews* 3:66–98.

Haughton B. G., King H. K. 1958. Toxopyrimidine phosphate as an inhibitor of bacterial enzyme systems that require pyridoxal phosphate. *Biochemical Journal* 70:660–665.

Helliwell K. E., Wheeler G. L., Smith A. G. 2013. Widespread decay of vitamin-related pathways: coincidence or consequence? *Trends in Genetics* 29: 469–478.

Henry M., Massey A. E. 1911. Some neglected sheep diseases of New South Wales. *Agricultural Gazette of New South Wales* 22:109–117.

Honeyfield D. C., Hinterkopf J. P., Brown S. B. 2002. Isolation of thiaminase-positive bacteria from alewife. *Transactions of the American Fisheries Society* 131: 171–175.

Honeyfield D. C., Brown S. B., Fitzsimons J. D., Tillitt D. E. 2005a. Early mortality syndrome in Great Lakes salmonines. *Journal of Aquatic Animal Health* 17:1–3.

Honeyfield D. C., Hinterkopf J. P., Fitzsimons J. D., Tillitt D. E., Zajicek J. L., Brown S. B. 2005b. Development of thiamine deficiencies and early mortality syndrome in lake trout by feeding experimental and feral fish diets containing thiaminase. *Journal of Aquatic Animal Health* 17:4–12.

Honeyfield D. C., Ross J. P., Carbonneau D. A., Terrell S. P., Woodward A. R., Schoeb T. R., Perceval H. F., Hinterkopf J. P. 2008. Pathology, physiologic parameters, tissue contaminants, and tissue thiamine in morbid and healthy central Florida adult American alligators. *Journal of Wildlife Diseases* 44:280–294.

James S. 1980. Thiamine uptake in isolated schizonts of *Eimeria tenella* and the inhibitory effects of amprolium. *Parasitology* 80:313–322.

Jenkins A. H., Schyns G., Potot S., Sun G., Begley T. P. 2007. A new thiamin salvage pathway. *Nature Chemical Biology* 3:492–497.

Jurgenson C. T., Begley T. P., Ealick S. E. 2009. The structural and biochemical foundations of thiamin biosynthesis. *Annual Review of Biochemistry* 78:569–603.

Kimura R. 1965. Thiamine decomposing bacteria. Pages 255–274 in *Review of Japanese Literature on Beriberi and Thiamine*, edited by K. Shimazono and E. Katsura. Kyoto (Japan): Vitamin B Research Committee of Japan.

Koski P., Pakarinen M., Nakari T., Soivio A., Hartikainen K. 1999. Treatment with thiamine hydrochloride and astaxanthine for the prevention of yolk-sac mortality in Baltic salmon fry (M74 syndrome). *Diseases of Aquatic Organisms* 37:209–220.

Kraft C. E., Gordon E. R. L., Angert E. R. 2014. A rapid method for assaying thiaminase I activity in diverse biological samples. *PLOS ONE* 9:e92688.

Kreinbring C. A., Remillard S. P., Hubbard P., Brodkin H. R., Leeper F. J., Hawksley D., Lai E. Y., Fulton C., Petsko G. A., Ringe D. 2014. Structure of a eukaryotic thiaminase I. *Proceedings of the National Academy of Sciences of the United States of America* 111:137–142.

Kurata A., Kadota H. 1981. Annual changes of vitamin B_1, biotin and vitamin B_{12} in water in Lake Biwa. *Journal of Nutritional Science and Vitaminology* 27: 301–309.

Landergren P., Vallin L., Westin L., Amcoff P., Börjeson H., Ragnarsson B. 1999. Reproductive failure in Baltic Sea trout (*Salmo trutta*) compared with the M74 syndrome in Baltic salmon (*Salmo salar*). *Ambio* 28:87–91.

Lawhorn B. G., Mehl R. A., Begley T. P. 2004. Biosynthesis of the thiamin pyrimidine: the reconstitution of a remarkable rearrangement reaction. *Organic and Biomolecular Chemistry* 2:2538–2546.

Linklater K. A., Dyson D. A., Morgan K. T. 1977. Faecal thiaminase in clinically normal sheep associated with outbreaks of polioencephalomalacia. *Research in Veterinary Science* 22:308–312.

Linster C. L., Van Schaftingen E., Hanson A. D. 2013. Metabolite damage and its repair or pre-emption. *Nature Chemical Biology* 9:72–80.

Lu J., Frank E. L. 2008. Rapid HPLC measurement of thiamine and its phosphate esters in whole blood. *Clinical Chemistry* 54:901–906.

Maier G. D., Metzler D. E. 1957. Structures of thiamine in basic solution. *Journal of the American Chemical Society* 79:4386–4391.

Manzetti S., Zhang J., van der Spoel D. 2014. Thiamin function, metabolism, uptake, and transport. *Biochemistry* 53:821–835.

McCandless D. W. 2010. *Thiamine Deficiency and Associated Clinical Disorders.* New York: Humana Press.

McCleary B. V., Chick B. F. 1977. The purification and properties of a thiaminase I enzyme from nardoo (*Marsilea drummondii*). *Phytochemistry* 16:207–213.

McDonald G., Fitzsimons J. D., Honeyfield D. C. 1998. *Early Life Stage Mortality Syndrome in Fishes of the Great Lakes and Baltic Sea.* Bethesda (Maryland): American Fisheries Society.

McRose D., Guo J., Monier A., Sudek S., Wilken S., Yan S., Mock T., Archibald J. M., Begley T. P., Reyes-Prieto A., Worden A. Z. 2014. Alternatives to vitamin B_1 uptake revealed with discovery of riboswitches in multiple marine eukaryotic lineages. *ISME Journal* 8:2517–2529.

Miller T. E., Burns J. H., Munguia P., Walters E. L., Kneitel J. M., Richards P. M., Mouquet N., Buckley H. L. 2005. A critical review of twenty years' use of the resource-ratio theory. *American Naturalist* 165: 439–448.

Mironov A. S., Gusarov I., Rafikov R., Lopez L. E., Shatalin K., Kreneva R. A., Perumov D. A., Nudler E. 2002. Sensing small molecules by nascent RNA: a mechanism to control transcription in bacteria. *Cell* 111:747–756.

Monteverde D. R., Gómez-Consarnau L., Cutter L., Chong L., Berelson W., Sañudo-Wilhelmy S. A. 2015. Vitamin B_1 in marine sediments: pore water concentration gradient drives benthic flux with potential biological implications. *Microbiological Chemistry and Geomicrobiology* 6:434.

Monteverde D. R., Gómez-Consarnau L., Suffridge C., Sañudo-Wilhelmy S. A. 2017. Life's utilization of B vitamins on early Earth. *Geobiology* 15:3–18.

Moore L. F., McLarty D. A. 1975. The influence of soil water extract and thiamine on the growth of *Cladophora glomerata*. *Canadian Journal of Botany* 53: 530–535.

Morris J. J., Lenski R. E., Zinser E. R. 2012. The Black Queen Hypothesis: evolution of dependencies through adaptive gene loss. *mBio* 3:e00036–12.

Moulin M., Nguyen G. T. D. T., Scaife M. A., Smith A. G., Fitzpatrick T. B. 2013. Analysis of *Chlamydomonas* thiamin metabolism in vivo reveals riboswitch plasticity. *Proceedings of the National Academy of Sciences of the United States of America* 110:14622–14627.

Murata K. 1965. Thiaminase. Pages 220–254 in *Review of Japanese Literature on Beriberi and Thiamine*, edited by K. Shimazono and E. Katsura. Kyoto (Japan): Vitamin B Research Committee of Japan.

Myers B. J. 1955. The rearing of a grey seal in captivity. *Canadian Field-Naturalist* 69:151–153.

Natarajan K. V. 1968. Distribution of thiamine, biotin, and niacin in the sea. *Applied Microbiology* 16:366–369.

Nishimune T., Watanabe Y., Okazaki H., Akai H. 2000. Thiamin is decomposed due to *Anaphe* spp. entomophagy in seasonal ataxia patients in Nigeria. *Journal of Nutrition* 130:1625–1628.

Nishimura T., Tanaka N. 1963. Biological studies on bacimethrin, a pyrimidine antibiotic, and monazomycin. *Journal of Antibiotics* 16:179–181.

Norrgren L., Andersson T., Bergqvist P.-A., Björklund I. 1993. Chemical, physiological and morphological studies of feral Baltic salmon (*Salmo salar*) suffering from abnormal fry mortality. *Environmental Toxicology and Chemistry* 12:2065–2075.

Ohwada K., Taga N. 1972. Vitamin B_{12}, thiamine, and biotin in Lake Sagami. *Limnology and Oceanography* 17:315–320.

Ohwada K., Otsuhata M., Taga N. 1972. Seasonal cycles of vitamin B_{12}, thiamine and biotin in the surface water of Lake Tsukui. *Nippon Suisan Gakkaishi* 38:817–823.

Okbamichael M., Sañudo-Wilhelmy S. A. 2005. Direct determination of vitamin B_1 in seawater by solid-phase extraction and high-performance liquid chromatography quantification. *Limnology and Oceanography: Methods* 3:241–246.

Paerl R. W., Bertrand E. M., Allen A. E., Palenik B., Azam F. 2015. Vitamin B_1 ecophysiology of marine

picoeukaryotic algae: strain-specific differences and a new role for bacteria in vitamin cycling. *Limnology and Oceanography* 60:215–228.

Pilátová M., Dionne M. S. 2012. *Burkholderia thailandensis* is virulent in *Drosophila melanogaster*. *PLOS ONE* 7:e49745.

Pritchard D., Eggleston G. W., Macadam J. F. 1978. Nardoo fern and polioencephalomalacia. *Australian Veterinary Journal* 54:204–205.

Propst K. L., Mima T., Choi K.-H., Dow S. W., Schweizer H. P. 2010. A *Burkholderia pseudomallei* ΔpurM mutant is avirulent in immunocompetent and immunodeficient animals: candidate strain for exclusion from select-agent lists. *Infection and Immunity* 78:3136–3143.

Provasoli L., Carlucci A. F. 1974. Vitamins and growth regulators. Pages 741–787 in *Algal Physiology and Biochemistry*, edited by W. D. P. Stewart. Oxford (United Kingdom): Blackwell Scientific Publications.

Ramos J. J., Marca C., Loste A., Jalón J. A. G. de, Fernández A., Cubel T. 2003. Biochemical changes in apparently normal sheep from flocks affected by polioencephalomalacia. *Veterinary Research Communications* 27:111–124.

Ramos J. J., Ferrer L. M., Garcia-Garcia L., Fernandez-Santander A., Loste A. 2005. Polioencephalomalacia in adult sheep grazing pastures with prostrate pigweed. *Canadian Veterinary Journal* 46:59–61.

Rasmussen N. 1999. The forgotten promise of thiamin: Merck, Caltech biologists, and plant hormones in a 1930s biotechnology project. *Journal of the History of Biology* 32:245–261.

Reddick J. J., Saha S., Lee J., Melnick J. S., Perkins J., Begley T. P. 2001. The mechanism of action of bacimethrin, a naturally occurring thiamin antimetabolite. *Bioorganic and Medicinal Chemistry Letters* 11: 2245–2248.

Richter C. A., Evans A. N., Wright-Osment M. K., Zajicek J. L., Heppell S. A., Riley S. C., Krueger C. C., Tillitt D. E. 2012. *Paenibacillus thiaminolyticus* is not the cause of thiamine deficiency impeding lake trout (*Salvelinus namaycush*) recruitment in the Great Lakes. *Canadian Journal of Fisheries and Aquatic Sciences* 69:1056–1064.

Rigdon R. H., Drager G. A. 1955. Thiamine deficiency in sea lions (*Otaria californiana*) fed only frozen fish. *Journal of the American Veterinary Medical Association* 127:453–455.

Rindi G., Ferrari G. 1977. Thiamine transport by human intestine in vitro. *Experientia* 33:211–213.

Robbins W. J. 1941. The pyridine analog of thiamin and the growth of fungi. *Proceedings of the National Academy of Sciences of the United States of America* 27:419–422.

Samruatruamphol S., Parsons H. T. 1955. An anti-thiamine effect produced in human subjects by bracken ferns. *Journal of the American Dietetic Association* 31: 790–793.

Sañudo-Wilhelmy S. A., Cutter L. S., Durazo R., Smail E. A., Gómez-Consarnau L., Webb E. A., Prokopenko M. G., Berelson W. M., Karl D. M. 2012. Multiple B-vitamin depletion in large areas of the coastal ocean. *Proceedings of the National Academy of Sciences of the United States of America* 109:14041–14045.

Sañudo-Wilhelmy S. A., Gómez-Consarnau L., Suffridge C., Webb E. A. 2014. The role of B vitamins in marine biogeochemistry. *Annual Review of Marine Science* 6:339–367.

Schaible U. E., Kaufmann S. H. E. 2004. Iron and microbial infection. *Nature Reviews Microbiology* 2:946–953.

Schauer K., Stolz J., Scherer S., Fuchs T. M. 2009. Both thiamine uptake and biosynthesis of thiamine precursors are required for intracellular replication of *Listeria monocytogenes*. *Journal of Bacteriology* 191:2218–2227.

Schmidhalter U., Evéquoz M., Studer C., Oertli J. J., Kahr G. 1994. Adsorption of thiamin (vitamin B_1) on soils and clays. *Soil Science Society of America Journal* 58:1829–1837.

Settembre E., Begley T. P., Ealick S. E. 2003. Structural biology of enzymes of the thiamin biosynthesis pathway. *Current Opinion in Structural Biology* 13:739–747.

Shimazono K., Katsura E. 1965. *Review of Japanese Literature on Beriberi and Thiamine*. Kyoto (Japan): Vitamin B Research Committee of Japan.

Shintani S. 1956. On the thiaminase disease of chickens. *Journal of Vitaminology* 2:23–30.

Stout F. M., Oldfield J. E., Adair J. 1963. A secondary induced thiamine deficiency in mink. *Nature* 197: 810–811.

Sudarsan N., Cohen-Chalamish S., Nakamura S., Emilsson G. M., Breaker R. R. 2005. Thiamine pyrophosphate riboswitches are targets for the antimicrobial compound pyrithiamine. *Chemistry and Biology* 12:1325–1335.

Suffridge C., Cutter L., Sañudo-Wilhelmy S. A. 2017. A new analytical method for direct measurement of particulate and dissolved B-vitamins and their congeners in seawater. *Frontiers in Marine Science* 4:11.

Tang Y. Z., Koch F., Gobler C. J. 2010. Most harmful algal bloom species are vitamin B_1 and B_{12} auxotrophs. *Proceedings of the National Academy of Sciences of the United States of America* 107:20756–20761.

Tasevska N., Runswick S. A., McTaggart A., Bingham S. A. 2008. Twenty-four-hour urinary thiamine as a biomarker for the assessment of thiamine intake. *European Journal of Clinical Nutrition* 62:1139–1147.

Thomas K. W. 1986. The effect of thiaminase-induced subclinical thiamine deficiency on growth of weaner sheep. *Veterinary Research Communications* 10:125–141.

Thomas K. W., Turner D. L., Spicer E. M. 1987. Thiamine, thiaminase and transketolase levels in goats with and without polioencephalomalacia. *Australian Veterinary Journal* 64:126–127.

Tillitt D. E., Zajicek J. L., Brown S. B., Brown L. R., Fitzsimons J. D., Honeyfield D. C., Holey M. E., Wright G. M. 2005. Thiamine and thiaminase status in forage fish of salmonines from Lake Michigan. *Journal of Aquatic Animal Health* 17:13–25.

Tilman D. 1988. *Plant Strategies and the Dynamics and Structure of Plant Communities*. Princeton (New Jersey): Princeton University Press.

Wang L., Wilkins J. H., Airth R. L. 1968. Repression of thiaminase I by thiamine and related compounds in *Bacillus thiaminolyticus*. *Canadian Journal of Microbiology* 14:1143–1147.

White J. R. 1970. Thiamine deficiency in an Atlantic bottle-nosed dolphin (*Tursiops truncatus)* on a diet of raw fish. *Journal of the American Veterinary Medical Association* 157:559–562.

Williams R. R. 1961. *Toward the Conquest of Beriberi*. Cambridge (Massachusetts): Harvard University Press.

Windheuser J. J., Higuchi T. 1962. Kinetics of thiamine hydrolysis. *Journal of Pharmaceutical Sciences* 51:354–364.

Winkler W. C., Cohen-Chalamish S., Breaker R. R. 2002. An mRNA structure that controls gene expression by binding FMN. *Proceedings of the National Academy of Sciences of the United States of America* 99: 15908–15913.

Wistbacka S., Heinonen A., Bylund G. 2002. Thiaminase activity of gastrointestinal contents of salmon and herring from the Baltic Sea. *Journal of Fish Biology* 60:1031–1042.

Wohlsein P., Peters M., Geburek F., Seeliger F., Böer M. 2003. Polioencephalomalacia in captive harbour seals (*Phoca vitulina*). *Journal of the American Veterinary Medical Association* 50:145–150.

Woolley D. W., White A. G. C. 1943a. Production of thiamine deficiency disease by the feeding of a pyridine analogue of thiamine. *Journal of Biological Chemistry* 149:285–289.

Woolley D. W., White A. G. C. 1943b. Selective reversible inhibition of microbial growth with pyrithiamin. *Journal of Experimental Medicine* 78:489–497.

Wooster G. A., Bowser P. R., Brown S. B., Fisher J. P. 2000. Remediation of Cayuga syndrome in landlocked Atlantic salmon *Salmo salar* using egg and sac-fry bath treatments of thiamine-hydrochloride. *Journal of the World Aquaculture Society* 31:149–157.

Worden A. Z., Follows M. J., Giovannoni S. J., Wilken S., Zimmerman A. E., Keeling P. J. 2015. Rethinking the marine carbon cycle: factoring in the multifarious lifestyles of microbes. *Science* 347:736–744.

Wrenger C., Eschbach M.-L., Müller I. B., Laun N. P., Begley T. P., Walter R. D. 2006. Vitamin B_1 *de novo* synthesis in the human malaria parasite *Plasmodium falciparum* depends on external provision of 4-amino-5-hydroxymethyl-2-methylpyrimidine. *Biological Chemistry* 387:41–51.

Wright J., Morley D. C. 1958. Encephalitis tremens. *The Lancet* 271:871–873.

Zallot R., Yazdani M., Goyer A., Ziemak M. J., Guan J.-C., McCarty D. R., de Crécy-Lagard V., Gerdes S., Garrett T. J., Benach J., Hunt J. F., Shintani D. K., Hanson A. D. 2014. Salvage of the thiamin pyrimidine moiety by plant TenA proteins lacking an active-site cysteine. *Biochemical Journal* 463:145–155.

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