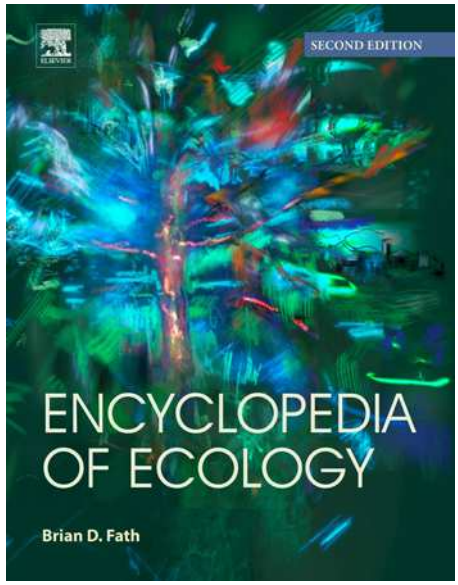

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Eco-Immunology: Past, Present, and Future

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A Brief History of Immunology

Immunology and especially ecoimmunology are young fields. Although Thucydides speculated as long ago as 400 BC about immunity after noticing that survivors of the plague became protected from second infections, the first true immunological study was by Ilya Methchnikoff who observed cellular defensive responses in starfish to wood splinters (Newell-McGloughlin and Re, 2006). By the 18th century in Europe (Riedel, 2005), immune processes were exploited in the interest of human health even though the mechanistic bases of protection were unknown. In ensuing years, Robert Koch, Louis Pasteur, and others improved such vaccination and other hygienic measures, although explicitly immunological insight, such as the distinction between humoral and cellular immunity, was not gained until the early 20th century (Tauber, 2003; Kaufmann, 2008).

By the mid 20th century, coincident with the molecular revolution, immunology grew rapidly including discoveries about tumor regulation, allergies, anaphylaxis, and the structure and synthesis of immunoglobulins. As many of these discoveries were made possible through the emergence of cellular and later molecular tools, immunology thrived as an almost exclusively reductionist discipline. Since its inception, the field focused predominantly on how host cells and tissues engaged various "dangerous" (Matzinger, 1994) and nonself (Burnet, 1961) threats, but recently, the emphasis has been made that such directives have shortcomings that might have affected the accumulation of knowledge (Tauber, 2017). For instance, important discoveries in other fields, such as the ability to classically condition immune responses (Ader and Cohen, 1982) and predict the size of disease epidemics using mathematics (Anderson and May, 1985), developed separately. Indeed, the field of epidemiology, which eventually instigated the discipline now recognized as disease ecology, has only recently and partly begun to merge with immunology (Brock *et al.*, 2014). Some immunology, namely vaccinology, is well integrated with epidemiology, but mostly intellectual pursuits about infectious disease biology have developed and operated independently of immunology (Tauber, 2017). The most striking distinction among infectious disease-related disciplines is how they deal with variation. Almost all immunologists have tried to control or eliminate it, going to extremes of breeding hosts in sterile conditions, standardizing genetic backgrounds, and/or attempting to ensure that temperature, diet, photoperiod, and other factors are identical among study groups. Most other disease biologists, and especially ecoimmunologists, instead strive to explain existing variation among or within hosts (Martin *et al.*, 2010). Ecoimmunologists (and "wild immunologists" sensu Pedersen and Babayan, 2011) study the defenses of thousands of different host species, oftentimes in their natural environments (Plowright *et al.*, 2008). For these immunologists, variation is the topic of interest.

Ecoimmunology Past

Ecoimmunology emerged from the work of behavioral ecologists interested in understanding elaborate sexual traits such as songs, ornaments, and mate-directed behaviors (e.g., courtship dances). Zahavi (1975) argued that these traits acted as handicaps, allowing females to use them as honest signals of male quality. The argument was that only mates of genuine high quality would be able to produce and keep such costly traits and achieve reproductive success too. Around the same time, Hamilton and Zuk (1982) extended the handicap hypothesis, proposing that male ornaments are good indicators of mate quality because the costs of elaborate traits should compromise the ability of males to combat infections (Hamilton and Zuk, 1982). If a male could maintain a large tail, produce an elaborate song, and/or execute a complicated display while infected, he would be a truly good male. Females should choose such males, especially if male traits had a genetic basis, which they often do. These ideas were later extended in the form of the immunocompetence handicap hypothesis (ICHH), which proposed a physiological mechanism for trade-offs between ornaments and immunity (Folstad and Karter, 1992). Observing that high levels of androgen hormones positively affected male ornamentation but negatively affected many immune functions, they proposed the first ecoimmunological hypothesis. They suggested that the benefits of testosterone for attracting mates were traded off against the adverse effects of testosterone on immunity, providing a mechanistic basis for handicaps. Although this hypothesis has since been tested extensively (Hunt *et al.*, 1997; Enstrom *et al.*, 1997) and in some sense launched the field of ecoimmunology, androgen effects on immune defenses are not as consistent as they originally conveyed (Arredouani *et al.*, 2014; Roberts *et al.*, 2004). Alternate versions of the ICHH have since been proposed and supported in organisms that do not use androgens (Nunn *et al.*, 2009), and these propositions, which are also based on eco-evolutionary principles (i.e., Bateman's hypothesis) explain intra- and interspecific immune variation reasonably well.

The term, ecological immunology, was first introduced in 1996 by Sheldon and Verhulst, and was proposed then as a valuable research area because most hosts remained susceptible to infections in spite of a strong history of selection by parasites. At the time, Sheldon, Verhulst, and others (Lochmiller and Deerenberg, 2000; Schmid-Hempel and Ebert, 2003) parroted a central

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proposition of evolutionary biology to justify ecoimmunology research: in most environments, resources are limited, so trade-offs should affect whether and how hosts defend themselves against infections. From that simple conjecture, the field developed rapidly (Martin *et al.*, 2011). Growth increased especially rapidly as the costs of immune defense became clear. It was long known that immune defenses required a supply of amino acids and calories (Beisel, 1977), but the eco-evolutionary ramifications of such costs were never before considered. In the livestock industry especially, the costs of immunity were well studied because of the economic consequences of breeding the largest and fastest growing, yet immunologically well-protected, animals. For these reasons, diet effects on immune functions were extensively studied in domesticated species (Klurfeld, 1993; Klasing, 2013). Not too long after Sheldon and Verhulst's call to action, data corroborating the costliness of immune defenses started to emerge from ecologists (Demas *et al.*, 1997; Martin *et al.*, 2003, 2007; Lochmiller and Deerenberg, 2000). The next steps were to probe whether such immune costs were large enough to lead to consequential trade-offs in nature (Norris *et al.*, 1994; Richner *et al.*, 1995).

In the ensuing 20 years, an enormous number of studies provided both correlative and experimental evidence revealing important costs of immunity for many vertebrates and invertebrates (Saino *et al.*, 1997; Festa-Bianchet, 1989; Graham *et al.*, 2010; Moret and Schmid-Hempel, 2000). Just this year, a metaanalysis involving many of these studies revealed significant costs of immunity for almost every taxon ever studied (Brace *et al.*, 2017). Songbirds and a few insects (i.e., bumblebees, *Drosophila* sp.) were the organisms of choice for much of the early work in this field. Several avian brood size experiments concluded that many measures of immune defense decreased with increasing reproductive output (Gustafsson *et al.*, 1994; Norris *et al.*, 1994; Norris and Evans, 2000). Trade-offs between immune function and other costly life processes, such as feather regrowth, were observed in domesticated chickens (Alodan and Mashaly, 1999), wild house sparrows (Martin, 2005), and other species. Even migratory disposition was found to impact immunity (Møller and Erritzøe, 1998), although results were mixed depending on several factors (Owen and Moore, 2006; van Gils *et al.*, 2007). Growth too was found to affect and be affected by immunity (Rivera *et al.*, 1998). Today, the costs of immunity and defenses generally are so ensconced in ecology (Connors and Nickol, 1991; Lochmiller *et al.*, 1993) that we no longer question their relevance. Now, we seek to understand whether and how their effects can percolate through communities (Beldomenico and Begon, 2010; Paull *et al.*, 2012).

Immunocompetence: The Ecoimmunologist's Red Herring

Coincident with the rise of ecoimmunology were frustration and healthy skepticism about the immunological tools of ecologists. What ecologists and organismal biologists wanted to measure was immunocompetence, or "how hosts prevent or control infections." What they used to describe such a complex trait were coarse measures at best (Adamo, 2004). This approach was understandably a frustration to traditional immunologists who spent years developing precise tools to characterize the responses of (mostly) murine immune systems to diverse viral, microbial, and metazoan threats. Most prominent among those first ecological tools was the phytohemagglutin (PHA) skin test. This assay was thought to quantify cell-mediated immunity and by extension serve as a measure of T-cell sensitive parasite control (Duffy and Ball, 2002; Faivre *et al.*, 2003; etc.). In practice, one injected a small amount of PHA (in solution) under the skin and measured resultant swelling using pressure-sensitive calipers. Although this technique revealed several surprising things about the immune systems of wild animals (e.g., seasonal variability in strength (Martin *et al.*, 2004) and nonlinear scaling with body mass (Tella *et al.*, 2002)), rarely were PHA measures related to control of a given infection, so its relevance as a metric of immunocompetence remained unclear. For these reasons, the PHA and related tests (i.e., leukocyte counts, quantification of total immunoglobulins) began to fall out of favor.

At that time, ecoimmunologists started to rely less on easy-to-use tools, instead favoring functional readouts of host protection or tools used in the labs of modern immunologists (Fassbinder-Orth, 2014; Boughton *et al.*, 2011). One assay involving agglutination of foreign red blood cells became quite popular (Deerenberg *et al.*, 1997); another involving the killing of various microbes by blood plasma and serum quickly grew in popularity (Millet *et al.*, 2007; Liebl and Martin, 2009). As ecoimmunologists started to accept that measuring single measures could never capture something as nebulous as immunocompetence (Martin *et al.*, 2006; Viney *et al.*, 2005), progress in the field grew. Not too long after, ecologists would propose new frameworks and concepts that would eventually spill into traditional immunology (Schmid-Hempel and Ebert, 2003; Viney *et al.*, 2005). Foremost among these was the concept of parasite tolerance (Råberg *et al.*, 2007).

Parasite tolerance emphasizes that hosts can cope with infection in a different manner than usually emphasized in immunology. Historically, immunology focused on mechanisms to regulate the numbers of parasites (i.e., resistance), just as a few behavioral ecologists had emphasized avoidance and other behaviors as a way to escape infection. The additional possibility, that hosts could mitigate parasite damage instead of controlling parasite burden (Medzhitov *et al.*, 2012), had never really been embraced, perhaps because as a predominantly biomedical field the thought of permitting enduring infections was too distasteful to pursue (Acevedo-Whitehouse and Cunningham, 2006; Hill, 2001; Schroder and Bowie, 2005). In the mid-20th century, though, plant biologists demonstrated quite clearly that hosts can cope feeding insects, fungi and other enemies better than trying to prevent exposure to these organisms altogether. Animal biologists eventually co-opted this concept, defining parasite tolerance mathematically as the relationship between host fitness or performance and parasite burden (Roy and Kirchner, 2000; Råberg *et al.*, 2009). Today, research on parasite tolerance abounds and includes studies that attempt to refine its measurement (Louie *et al.*, 2016), resolve its mechanistic basis (Sears *et al.*, 2011; Ayres and Schneider, 2012; Soares *et al.*, 2017; Medzhitov *et al.*, 2012), and elucidate its eco-evolutionary effects at levels of biological organization above individuals (Gervasi *et al.*, 2017; Johnson and Levin, 2013).

Ecoimmunology Present

From Immunocompetence to Host Competence

Ecoimmunology continues to be a popular field, as evidenced by the many reviews (Little *et al.*, 2012; Demas and Nelson, 2011; Demas *et al.*, 2011; Adamo, 2004; Raffel *et al.*, 2008; Martin, 2009; Martin *et al.*, 2006, 2010; Adelman and Martin, 2009; Ezenwa *et al.*, 2016) of its history, purview, and implications. Of the many concepts that currently captivate researchers, one, host competence (i.e., the propensity of an individual to generate infections in another individual) is facilitating integration with other disease research at multiple levels of biological organization (Gervasi *et al.*, 2015, 2017; Barron *et al.*, 2015; Martin *et al.*, 2016; Keesing *et al.*, 2012; Luis *et al.*, 2013). Competence is underlain by many physiological and behavioral characteristics that affect exposure, elimination, and subsequent transmission of a parasite (Ferrari *et al.*, 2004). Variability in host competence within and among individuals and species can contribute to spatiotemporal heterogeneity in disease at the community level (Barron *et al.*, 2015; Gervasi *et al.*, 2015; Martin *et al.*, 2017). To date, there have been two prime ecological areas of study with regards to competence: the dilution effect and superspreading.

The first, the dilution effect, represents the recurrent observation that host diversity often reduces disease risk (Civitello *et al.*, 2015; Ostfeld and Keesing, 2000). Although the scale of study and other factors can eliminate or even reverse the effects of biodiversity on disease risk (Wood *et al.*, 2014), dilution effects are common enough (LoGiudice *et al.*, 2003; Keesing *et al.*, 2010; Ezenwa *et al.*, 2006) that many have been motivated to investigate their mechanistic bases. Prime among them is heterogeneity in host competence. Potential hosts in an environment differ dramatically in their ability to replicate parasites (Schmidt and Ostfeld, 2001). To date, the Lyme disease system has been best-studied with regards to the role of competence in dilution effects. Lyme disease is caused by infections with the bacterium, *Borrelia burgdorferi* (Bb), with is transmitted by ixodid ticks. A few mammalian hosts are much more competent than others and play important roles in the local dynamics of Lyme disease. The white-footed mouse (*Peromyscus leucopus*) is especially competent for Bb, and its immune system and particularly its antimicrobial responses are quite distinct from other mammals (Previtali *et al.*, 2012), even other *Peromyscus* (Martin *et al.*, 2007, 2008). What is also particularly compelling and somewhat concerning about this and similar species is that it is competent for multiple tick-borne, disease-causing microbes (Ostfeld *et al.*, 2014). Intriguingly, variation in competence can be predicted by the life history and behavioral traits of hosts, phenomena that provide opportunities for the mitigation of human disease risk and perhaps even predictions about under- or unstudied species in new ecosystems or novel parasites (Han *et al.*, 2015). Evidence is gathering in other systems, such as vertebrate-trematode, snail-trematode, vertebrate-fungal, and plant-fungal systems, that the most abundant and widespread hosts, with life-history traits that favor reproduction and dispersal, are often the most competent (Johnson *et al.*, 2012; Sears *et al.*, 2015; Venesky *et al.*, 2014; Lively and Dyndahl, 2000; Parker *et al.*, 2015).

A second reason ecologists are now interested in host competence is embodied in the hallmark superspreader, Mary Mallon, better known as Typhoid Mary (Soper, 1939). Typhoid Mary was said to be responsible for the infections of 22 people, which proved fatal for three of those individuals. As an asymptomatic typhoid fever carrier, Mary came into contact with many others while working as a cook. Typhoid Mary is not an aberration it seems. Superspreaders appear to be important for other diseases, such as acute respiratory syndrome, or SARS, which first emerged in late 2002 and rapidly spread via air travel through May 2003. There were nearly 8000 reported cases of SARS (Riley *et al.*, 2003), but transmission events varied quite extensively across patients. Patient A, the first known infected patient, reportedly transmitted the SARS pathogen to 33 other individuals (Shen *et al.*, 2004). Scientists concluded that SARS was likely transmitted to three other individuals, all of whom infected more than eight additional people (Shen *et al.*, 2004).

Although only recently emphasized, superspreaders might be common in many host-parasite systems (Lloyd-Smith *et al.*, 2005; Kilpatrick *et al.*, 2006) including tuberculosis and measles outbreaks (Stein, 2011). Indeed, the 20:80 rule in epidemiology highlights that 20% of infected individuals tend to be responsible for 80% of new infections (Woolhouse *et al.*, 1997). Methods for identifying these keystone individuals are only just being developed (Modlmeier *et al.*, 2014; Paull *et al.*, 2012), and often identification is quite hard to do because hard-to-quantify behavioral differences are what distinguishes hosts. Mechanistically, though, there are several promising avenues to consider as biomarkers, and there is a large need for such work, as competence can be quite labile in some species (Gervasi *et al.*, 2016). In other words, whereas host species vary quite a bit in their competence, individual hosts within species too could be quite different too. Various natural and anthropogenic stressors, resource depletion, habitat quality, and other factors could alter the traits that hosts use to cope with infections (Gervasi *et al.*, 2015; Martin *et al.*, 2010). For instance, glucocorticoids, which have profound and diverse effects on immune function (Martin, 2009), dramatically altered the ability of avian hosts to serve as competent reservoirs for West Nile virus. Birds with chronically (surgically) elevated stress hormones were 2 × more attractive (Gervasi *et al.*, 2016) and enduringly more infectious (Gervasi *et al.*, 2017) to biting vectors than controls. Some of these effects were related to the expression of cytokines (e.g., interferon gamma), molecules expressed by leukocytes and other cells that directly antagonize parasites or coordinate cellular defenses (Martin *et al.*, 2016).

Causes and Consequences of Co-Infection

Another growing area of interest in ecoimmunology and a prime example of the ongoing merger between ecoimmunology and disease ecology (Hawley and Altizer, 2011; Brock *et al.*, 2014) involves co-infections. In the wild, it is probably much more common to be infected by many versus a single pathogen, which makes the common practice in immunology to study one

parasite alone naturally unrepresentative. When a host is co-infected, interactions between pathogens can alter the outcome of infections (Corbett *et al.*, 2003; Bromenshenk *et al.*, 2010; Johnson and Hoverman, 2012). Pathogens can interact directly, competing for resources or space (Kuris and Lafferty, 1994), but they can also interact indirectly, through the immune system (Sousa, 1992). The best known and most extreme example of co-infection in hosts and how the immune system can play a role in the outcome of disease entails the human immunodeficiency virus, HIV (Shankar *et al.*, 2014; Moreno *et al.*, 2000; Abu-Raddad *et al.*, 2006). HIV reduces the functionality of the host immune system, leaving the host open to secondary infections. For instance, co-infection with HIV and tuberculosis (TB) accelerates the deterioration of the host immune system and increases the negative effects of both pathogens (Shankar *et al.*, 2014). Patients with leishmaniasis and HIV experienced more relapses in leishmaniasis symptoms after treatment with pentavalent antimony than individuals who were not co-infected (Moreno *et al.*, 2000). Co-infected individuals had significantly lower levels of serum transforming growth factor-beta (TGF-β1; Moreno *et al.*, 2000). The authors postulated that the lower levels of TGF-β1 and the host's inability to mount a leishmaniasis-specific immune response could be the reason for more common relapses (Moreno *et al.*, 2000). Co-infection with HIV and malaria has been shown to increase transmission of both of these pathogens. HIV facilitates malaria transmission and infection with malaria strongly activates CD4 cells, which then facilitates HIV transmission because HIV can replicate rapidly in the CD4 cells (Alemu *et al.*, 2013).

Outcomes of co-infection can be dependent on the host's immune resource allocation and, as described above, the type of immune response necessary to combat the infections in question (Alemu *et al.*, 2013; Graham, 2008; Sousa, 1992). In situations where resources allocated to the host's immune response are limited, mounting a sufficient immune response can be challenging. This is particularly true in cases where the immune system mounts differing responses to the pathogens from different taxa. Given limited resources or a lack of coevolutionary history between host and pathogen (Graham, 2002; Graham *et al.*, 2005), activating and maintaining two distinct immune pathways might be impossible. Subsequently, co-infection could have greater impacts on hosts or even host populations than single infections. For instance, in African buffalo (*Syncerus caffer*), co-infection with bovine tuberculosis (BTB) and gastrointestinal helminths decreased mortality risk in individual buffalo. Individuals infected with BTB alone had higher levels of interferon gamma (IFN-y) than individuals that were coinfected with worms. Altogether, interactions between these two infections led to higher prevalence of helminth infections in the population because of the effect of BTB on host immune systems (Ezenwa and Jolles, 2015).

Co-infection with similar pathogens can also increase disease burden. Co-infection of murine hosts with *B. burgdorferi* and *Ehrlichia bacteria*, the causative agent of Granulocytic Ehrlichiosis, increased pathogen loads and Lyme arthritis severity relative to hosts infected with *B. burgdorferi* alone. Co-infected hosts also had lower levels of interleukin-12 (IL-12), interferon-y (IFN-y), and fewer INF-y receptors on macrophages. These Th1-type cytokines are typically upregulated to combat bacterial infections. Conversely, they saw an increase in interleukin-6 (IL-6) levels with co-infection (Thomas *et al.*, 2001). Increases in IL-6 levels can decrease the effects of Lyme arthritis in C57BL/6 mice (Anguita *et al.*, 1996), which means that despite increased burden, this immune response might decrease symptoms. Indeed, co-infections with similar pathogens need not always increase disease burden. Co-infections with similar pathogens could foster cross immunity in hosts. In these cases, parasites are so similar that host responses to one infection will be protective against subsequent infections. For example, when mice were infected with genetically distinct clones of rodent malaria, the primary infecting clone established. However, if the secondary infecting clone was added after the primary infection had established, the secondary clone did not reach as high a burden (de Roode *et al.*, 2005). Moreover, exposure to like pathogens at similar times can cause a more rapid or larger magnitude systemic response. This scenario could lead to more rapid and effective protection against both pathogens. Co-infections are known alter host immunity (Thomas *et al.*, 2001; Moreno *et al.*, 2000), which in turn, can change the outcome of infection and increase pathogen transmission between hosts (Alemu *et al.*, 2013; Ezenwa and Jolles, 2015). Ecoimmunologists are working to better understand how pathogen interactions are immune-mediated and how co-infections alter transmission dynamics and population disease dynamics.

Ecoimmunology Future

The above text about dilution effects, superspreading, and coinfections highlights the need to understand the effects of anthropogenic change on disease in natural systems. Since the inception of the field, scientists have probed how global changes will affect immune responses of individuals and the impacts of these effects on populations and communities (Martin *et al.*, 2010; Martin and Boruta, 2014). For years now we have known that reproduction, molt, migration, and development all induce context-dependent costs on an individual, and these costs affect their ability to respond to infections (Brace *et al.*, 2017). Ongoing, escalating global changes are apt to alter or sometimes even exacerbate immune-related trade-offs. For example, amphibian species that reside in human-impacted forest exhibit reduced bactericidal killing ability (Hopkins and DuRant, 2011). Poor habitat quality and resource scarcity also correlate with land development (Klurfeld, 1993; Moret and Schmid-Hempel, 2000; Cropper and Griffiths, 1994), and these factors are known from other fields to affect immune responses (Glick *et al.*, 1981). Habitat destruction is not the sole consequence of human disturbance in several circumstances. There is evidence that chemical toxins affect susceptibility to pathogens (Ross *et al.*, 2000). In a metaanalysis, pesticide exposure at environmentally relevant levels was shown to decrease immune function and increase pathogen load in fish and amphibians (Rohr and McCoy, 2010). Pesticides have been shown to decrease a variety of immune functions in these taxa including decreases in proliferative activity of B and T lymphocytes (Rymuszka *et al.*, 2007), lower levels of melano-macrophages in the liver, eosinophils in the blood (Rohr *et al.*, 2008), and total white blood cell counts (Christin *et al.*, 2004).

In its short lifespan, ecoimmunology has made many important contributions and begun to merge with disease ecology to produce one of the most integrated biological research fields (Brock *et al.*, 2014; Ezenwa *et al.*, 2016). Going forward, an integrated disease ecology promises to have more positive impacts on our understanding of immune variation among and within species, which could be helpful in medicine, mitigation of global climate change effects, and management and prevention of zoonotic and other disease outbreaks (Tauber, 2017).

See also: Ecological Data Analysis and Modelling: Forest Models. Ecological Processes: Evolution of Parasitism. Evolutionary Ecology: Red Queen Dynamics. General Ecology: Parasites; Ecophysiology. Global Change Ecology: Xenobiotic (Pesticides, PCB, Dioxins) Cycles

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