

Definitions of parasites and pathogens through time

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Abstract

Scientists ought to apply universally accepted definitions to technical terms to enable precise communication and discussion. Throughout history, many definitions have shifted, such as those of important terms in evolutionary biology, modes of life, and the nature of interactions. Conversely, throughout history, important terms have been used without proper definition. Two such terms are parasites and pathogens. An extensive body of literature considers parasites and pathogens to be categorically negative, which has resulted in definitions that lack objectivity and limit a full understanding of the biology of these organisms. Different interpretations have resulted in shifting definitions, in turn causing confusion. Here, we present the remarkable history of both definitions, an overview of alternative definitions put forward throughout history, and a working definition for both terms. We find that the line between what is a parasite or a pathogen is often blurry, and is additionally complicated due to the multi-modal nature of interactions.

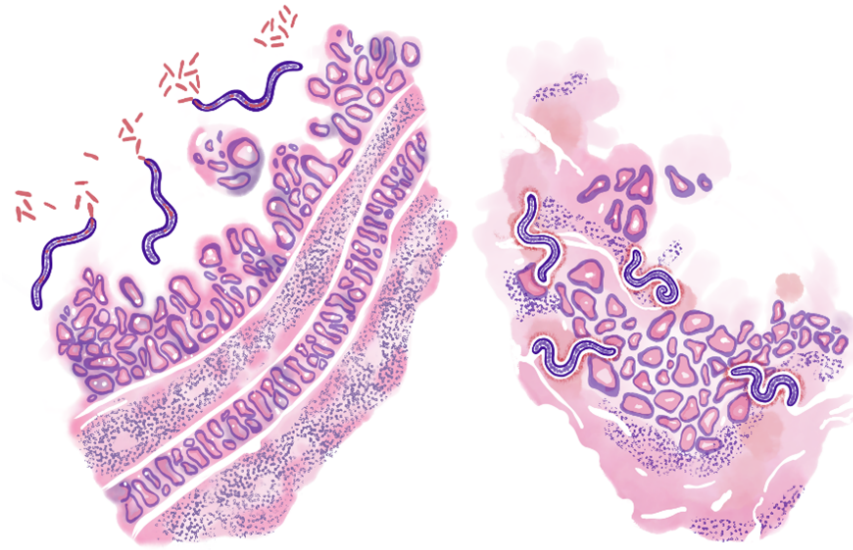


Figure 1: An artist’s impression of nematodes in human colon cells to demonstrate the perceived duality of parasites. Do they protect us from harmful microbes or are they themselves harmful? On the left, the nematodes protect the colon tissue from harmful microbes. On the right, the nematodes are the harmful parasites. Illustration by Vera Williams and Alana van den Berg.

Introduction

There are an estimated 8.7 million multicellular species of organisms on planet Earth (Mora *et al.*, 2011). With roughly 1.2 million currently valid species, this means that 86% of existing species are still to be described. Basic classification is an indispensable step in understanding organisms and their modes of life. Therefore, scientists need to ensure technical terms are correct with universally accepted definitions. Throughout scientific history, many definitions have shifted. Examples are definitions of important terms in evolutionary biology, modes of life, and the nature of interactions, such as “symbiosis” (Leung and Poulin, 2008) and “microbe” (Hariharan, 2021). In this chapter, we will trace the remarkable history of parasitology and pathology in order to explore the definitions of *parasite* and *pathogen* through time.

Central to the exploration of parasitological and pathological history is the understanding that most people consider parasites and pathogens to be categorically negative. Approaching the subject through this lens has led to definitions that lack objectivity and limit a full understanding of the organism’s biology (**Fig. 1; Tables 1, 2**). This has caused misinterpretations and confusion and will be addressed in this chapter. Here, we regard parasites as multicellular organisms that live at the expense of a single host reducing its fitness but not directly causing death (*sensu* Haelewaters *et al.*, 2017), and pathogens as microorganisms capable of producing disease under normal conditions of host resistance and rarely living in close association with the host without producing disease (*sensu* Onstad *et al.*, 2006).

Parasitology throughout the literature

The original definition of parasite came from the Greek *parasitos*, “(someone) eating at another’s table,” with *para* meaning beside and *sitos* meaning food or grain. The word was applied negatively to a person who gleaned meals from the wealthy in exchange for flattery, and later more generally for sycophants and toadies (Brooks and McLennan, 1993; Harant, 1995). Posidonius (c. 135 – c. 51 BCE), a Greek historian

who traveled to Gallia, mentions that the Celtic chieftains had “parasites,” servants who followed them around and sing the chieftains’ praises during social gatherings (Tierney, 1959). In *Coriolanus*, a play by Shakespeare written in 1608, “parasite” is used to refer to obsequious courtiers.

Advances in microscopy starting in the 16th century enabled numerous observations of microscopic organisms living in and amongst the tissues of larger organisms. Knowledge of parasites in the biological sense appeared in the 17th century, first pertaining to parasitic plants such as mistletoe (Grew, 1681). This marked a shift from the term being used as a social descriptor of interactions between humans, to include non-human systems: “something feeding off another.” This scientific definition of parasite entered common parlance in the 18th century, but it was already imbued with a negative social tone. This interplay between social and scientific definitions of the word parasite means that a scientifically neutral term has a negative connotation for a general audience (Musolff, 2014).

Fossilized material including human feces has shown that early human ancestors were often infected with parasites (Camacho *et al.*, 2018). The earliest known example of a human parasite was lung fluke (*Paragonimus* sp.) eggs found in fossilized feces in northern Chile. These fossils were estimated to be from 5900 BCE (Horne, 1985). Evidence of the malaria-causing protozoan parasite *Plasmodium falciparum* has been preserved in the famous mummy of the Egyptian pharaoh Tutankhamun (c. 1341 – c. 1323 BCE), which may have been the cause of his early death (Hawass *et al.*, 2010). We can, however, not know for certain when the first parasites were observed as the oldest known script, the so-called cuneiform script, was only developed around 3400 BC (Schmandt-Besserat, 2015).

Parasites visible to the naked eye were described in ancient cultures such as Ancient Greece and Ancient Rome (Hoepli, 1956), including descriptions by Aristotle (Hugo *et al.*, 2001). According to the translation by Camus (1783), helminths were described as “[worms that] grow in the feces of animals, either before or after the feces have been released from their gut. These are three kinds, the flat worms, the round worms, and the ascarids. These kinds can particularly be found in the human body.” Urinary myiasis, an invasion of the urinary tract by dipteran larvae, had been recorded in ancient Rome by Plutarch, who described a small animal with the morphology of a *Fannia* larva in the sperm of a man (Hoepli, 1956).

Having observed that ill effects often followed the consumption of pigs, both Islam and Judaism prohibit the consumption of pork. Scholars of these Abrahamic religions have connected these effects to what would eventually be understood as the muscle-infecting nematode, *Trichinella* (Neghina *et al.*, 2012). This painful parasite can be transmitted through the consumption of undercooked meat, forming calcified cysts in mammalian muscles. For hundreds of years, the cause of this ailment was unknown, and the custom of pork prohibition became firmly entrenched in these religions.

In Medieval Europe, parasites were believed to be generated in “corrupt matter,” a process called spontaneous generation (**Fig. 2**). For instance, Gilbert Anglicus explained that worms in the gut arose when a patient developed an excess of phlegmatic humors (Henderson, 1918). He prescribed bitter, aromatic, or acid mixtures from plants to kill the worms and expel them by inducing diarrhea (Henderson, 1918).

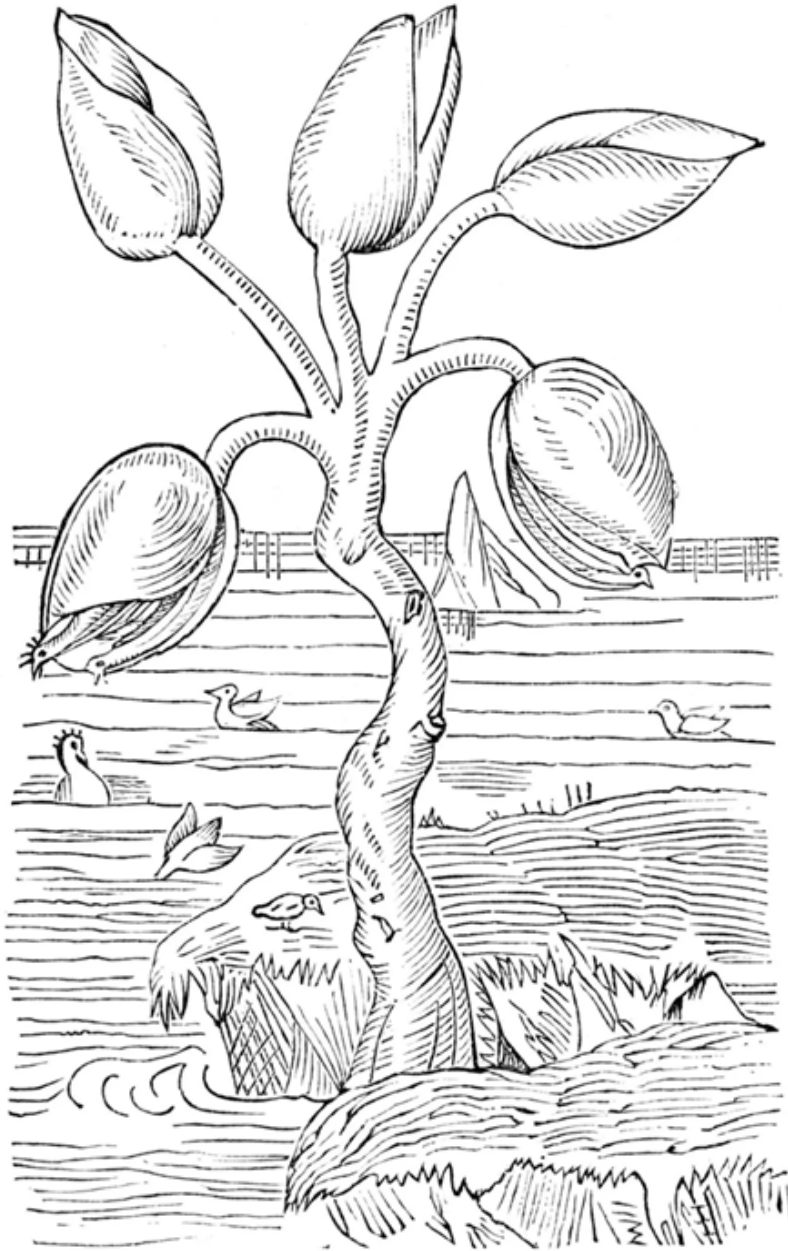


Figure 2: Barnacle geese (*Branta leucopsis*) were assumed to be developed from goose barnacles (*Pedunculata*) by spontaneous generation, as nests were never found in temperate Europe. Additionally, goose barnacles were thought to be attached to branches before falling in the water because goose barnacles were often found on driftwood. Wood engraving depicting a “goose-tree” from John Gerard’s (1597) Herball or Generall Historie of Plantes.

Following the invention of microscopes, Francesco Redi (1668) described external parasites for the first time. Amongst others, he described nasal flies of deer (*Cephenemyiinae* larvae) and the sheep liver fluke (*Fasciola hepatica*). One of his most significant contributions was his contradiction to the spontaneous generation theory. Redi tested the spontaneous creation of maggots via fresh meat in two jars; one jar was left open,

while the other jar was closed with a cloth. His experiment demonstrated that maggots do not emerge from meat, but instead that maggots came from fly eggs. In 1681, Antonie van Leeuwenhoek, the founder of microbiology, wrote in a letter to Robert Hooke that he had found “animalcules” in his stool. These cells were most likely *Giardia lamblia* trophozoites (Feely *et al.*, 1984).

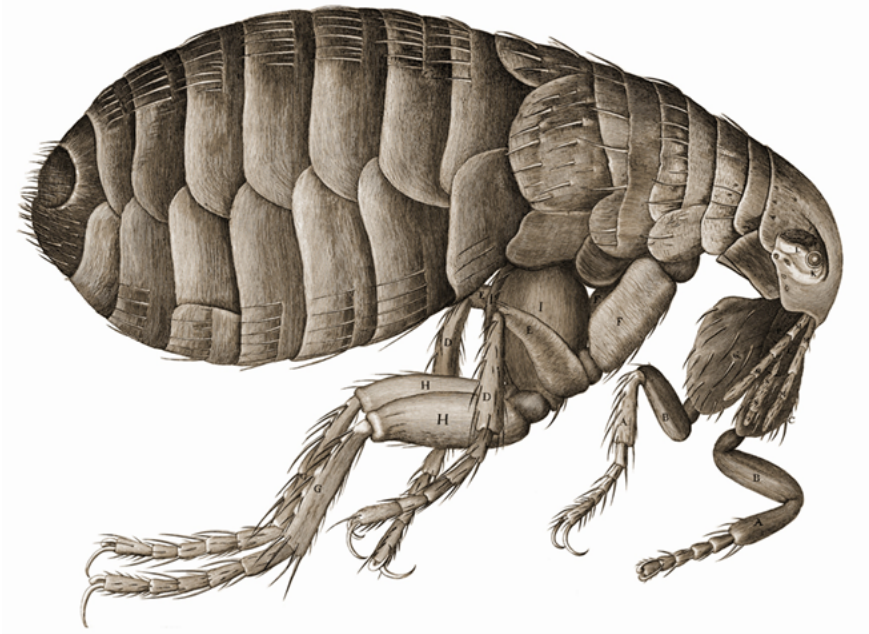


Figure 3: A flea (*Pulex irritans*) from Robert Hooke’s (1665) *Micrographia: or some Physiological Descriptions of minute bodies made by magnifying glasses. With Observations and Inquiries thereupon*. Hooke was the first to publish illustrations of organisms seen through microscopes, including parasites.

In the late 18th century, spontaneous generation was still a widely accepted hypothesis for parasites. For instance, physician Marcus Elieser Bloch stated that parasitic worms were destined to live in very specific locations within the host (Farley, 1992). He hypothesized that these parasites could not possibly arrive there by chance, rather, they had to arise from the host itself. In the early 19th century, Johann Bremser stated that parasitic worms did not occur elsewhere than inside the bodies of other animals. Therefore, he argued that these worms must be produced inside the body. As vectors and intermediate hosts were not yet known, opponents of the spontaneous generation theory could not substantiate their hypotheses.

By the 19th century, scientists realized that animals could develop in various ways previously unimagined. For instance, certain insect life cycles were observed for the first time. The larval and pupal forms were a departure from the well-known egg-to-adult pattern observed in many vertebrate life cycles. Other life cycles were also observed in benthic invertebrates, where larval stages had a contrasting morphology compared with the adult animals, for which they first had to undergo a complex metamorphosis. In 1842, Japetus Steenstrup, a Danish naturalist, made a crucial discovery: alternation of generations, also known as metagenesis or heterogenesis, in parasites (Farley, 1992). This life cycle involves transitioning between two forms, the asexual stage and the sexual stage. Steenstrup observed that the “immature” stage did not directly transform into a subsequent stage, but instead reproduced to generate more than one member to the next stage (Steenstrup, 1845).

Key elements for our story are his observations in flukes (Trematoda). It was known that flukes developed from cercariae, free-living larvae. He concluded that these larvae arose in large numbers from saclike bodies in

snails (Steenstrup, 1845). These saclike bodies did not resemble the adult stage. As he was not interested in parasites per se, he was not aware that he introduced two major concepts for parasitology: the intermediate host and the parasitic life cycle. This field of research was investigated further by, amongst others, Friedrich Kuechenmeister, Carl von Siebold, and Pierre-Joseph van Beneden a few years later. They researched the life cycle of *Cystica*, a taxon of parasitic worms. As the *Cystica* worms lacked reproductive organs and were found nowhere else than muscles or the digestive system, they were the most obvious examples of spontaneous generation in worms (Farley, 1992). Their feeding experiments with tapeworms showed that *Cystica* was in fact a collection of larval stages of terrestrial tapeworms and that these worms have a complex life cycle (Farley, 1992).

Historical definitions of parasites

Understanding the word parasite requires context. Coined almost simultaneously by Albert Bernhard Frank (1877) and Heinrich Anton de Bary (1878), the term “symbiosis” is defined as a spectrum of interspecies interactions, ranging from mutualism to commensalism to parasitism. While some researchers have used the term symbiosis to refer only to mutualistic, or mutually beneficial relationships, there is precedent within mycology and other disciplines to deploy the term when referring to a spectrum—ranging from parasitism to commensalism to mutualism (Trappe, 2005; Leung and Poulin, 2008; Horton, 2015)—and this is the meaning invoked here. That being said, there is additional confusion around the term symbiosis, which, depending on the framework, could be considered an exception to biological norms, or a fundamental condition of life for most multicellular organisms.

Reference	Definition
Chandler (1961)	A form of symbiosis in which one species lives at the expense of the other
Webster’s Third New International Dictionary (1963)	An organism living in or on another living organism, obtaining from it part or all of its organic nutriment, commonly exhibiting some degree of adaptive modification, and causing some degree of real damage to the host.
Crofton (1971)	An ecological relationship between the populations of two different species with the following special features: (i) the infection process produces an over-dispersed distribution of parasites within the host population; (ii) the parasite kills heavily infected hosts; (ii) the parasite species has a higher reproductive potential than the host species.
Poulin (2007)	A close relationship between species, where one organism, the parasite, lives on or inside another organism, the host, causing it some harm, and is adapted structurally to this way of life.
Haelewaters <i>et al.</i> (2017)	Organisms living at the expense of a single host, which are multicellular (in contrast to pathogenic microorganisms) and do not directly cause death of the host (in contrast to parasitoids)

Table 1: Alternative definitions of the term parasite.

In the late 19th century, Frank (1885) introduced hypotheses on the mutualistic nature of mycorrhizal networks. Mycorrhizae are fungi that form partnerships with plants, in which the fungi typically supply the

plant with nitrogen, phosphate, water, and microbial defenses in exchange for photosynthate. These hypotheses were considered a challenge to conventional biological understanding when introduced and were therefore highly contested (Trappe, 2005). This unconventional lens was also applied to the fundamental association of fungi and algae in lichen biology, with mycologists such as Anton de Bary and Simon Schwendener arguing for a new framework for understanding this dynamic (Plitt, 1919; Kaishian and Djoulakian, 2020). More than a century later, these ideas are only just becoming well-integrated into scientific literature and lexicon, and remain poorly understood and under-recognized outside of mycology (Trappe, 2005).

With parasitism being understood as the other end of the symbiotic spectrum, the term parasite therefore refers to a loose group cheekily defined by Brooks and McLennan (1993) as “organisms studied by parasitologists.” Edward O. Wilson (2014) attempted to quantify the definition of parasite by saying, “parasites eat prey in units less than one.” Alternatively, parasites can be defined as organisms that “find their nourishment and habitat on other living organisms, without destroying it as predators do prey” (Brooks and McLennan, 1993). While that definition may seem appropriate at first blush, there are a number of organisms that do not fit that definition but have been traditionally considered parasites, such as *Oxyruida* nematodes (pinworms) that feed on intestinal bacteria and protozoa rather than host tissue (Adamson, 1994). Or, alternatively, there are a number of organisms that meet this definition but have not traditionally been considered parasites, such as vampire bats, mosquitoes, and perhaps most strikingly, herbivores. For instance, is a chrysomelid (leaf beetle) living on and eating a plant leaf parasitic? Conventional wisdom would say no.

In order to understand this dilemma, it is useful to consider the origins of the discipline of parasitology, which are situated in the context of disease biology. In addition to the social origins of the word discussed above, parasitology emerged around the same time as bacteriology, linking with research of pathogenicity and widely viewed within a non-Darwinian framework (Brooks and McLennan, 1993). Thus, parasites were historically approached and understood as unwanted, harmful organisms that disrupted the “natural” order of otherwise discrete and independent individuals. For example, nematodes are a ubiquitous group that fills a vast array of niches. The aforementioned pinworms living in the gastrointestinal tract of mammals, feeding not on host tissue but on bacteria and protozoa are, by definition, commensals. However, their nature as worms predisposes humans to view them as “lesser than,” and their presence within the bodies of mammals is understood negatively, and they are thus often considered parasites (**Fig. 1**).

The red-billed oxpecker: mutualist or parasite?

An interesting example of shifting definitions exists in the tension between the biology and perception of the red-billed oxpecker, *Buphagus erythrorhynchus* (**Fig. 4**). These birds live on the bodies of large African mammals, such as giraffes, rhinos, and zebras, feeding on ticks, dry skin, and exudates such as sweat and mucus (Weeks, 2000). Because ticks are understood to be harmful to their hosts, causing disease, infection, and metabolic drag, the relationship between the red-billed oxpeckers and the mammals was long thought to be mutualistic: the mammals benefit from having the ticks removed and in turn, the birds benefit with a meal. Birds—due to their status as popular, beloved organisms—are not typically associated with parasitism. Therefore, the red-billed oxpecker’s positive status as “mutualist” in this system went widely reported but uninterrogated in the literature. However, Weeks (2000) conducted the first quantitative study of the relationship between oxpeckers and ticks on host cattle, and found that adult tick loads on the cattle are not impacted by the presence or absence of the birds. Moreover, the presence of the birds actually prolong the healing time of wounds on cattle. Then again, a recent study by Plotz and Linklater (2020) added one more piece of the puzzle by showing experimentally that rhinos use oxpeckers alarm calls to detect and evade humans undetected. These findings significantly complicate the categorization of the red-billed oxpecker as either or. It becomes evident that these interactions are complex and multi-faceted.



Figure 4: Red-billed oxpecker (*Buphagus erythrorhynchus*) on a giraffe (*Giraffa* sp.) in South Africa. Photo: Bernard Dupont, Wikimedia Commons.

Historical definitions of pathogens

The earliest recorded epidemic occurred during 430 BCE amidst the Peloponnesian War (Retief and Cilliers, 1998). This disease, suspected to have been typhoid fever, spread through Libya, Ethiopia, and Egypt, to eventually hit both the Athenians as well as the Spartans, and an estimated two-thirds of the population died (Retief and Cilliers, 1998; Littman, 2009). During this time, the miasma theory (advanced by Hippocrates of Kos) was widely accepted as an explanation for diseases. The theory posited that a nebulous “miasma” emerged from rotting organic materials and made people ill.

The basic tenets of Germ theory—the idea that growth and reproduction of microorganisms can cause disease—was first reported by Islamic physicians in the Islamic Golden Age. In his famous work *Canon of Medicine* (1025), Abu Ali Sina (also known as Ibn Sina or Avicenna) claimed that a quarantine (a period of 40 days) was essential to prevent further spread of contagious infections (Whinder, 2012). Over 500 years later, European scientists started to arrive at similar conclusions. In his 1546 work *De Contagione et Contagiosis Morbis* [On Contagion and Contagious Diseases], Girolamo Fracastoro suggested that infections could result from tiny, self-multiplying “bodies.” These bodies could be spread by direct or indirect contact through infected objects or could even be passed through the air over long distances. In 1762, physician Marcus von Plenciz hypothesized that each disease was caused by a different organism dwelling within the human body—a hypothesis later proven by, amongst others, Robert Koch.

Reference(s)	Definition
Ford (1927)	A microorganism that can increase in living tissue and produce disease.
Smith (1934)	A parasite capable of causing or producing some disturbance in the host.
Smilack (1980), Hoepflich (1989)	A microbe capable of causing disease.
Falkow (1997)	Any microorganism whose survival is dependent upon its capacity to replicate and persist on or within another species by actively breaching or destroying a cellular or humoral host barrier that ordinarily restricts or inhibits other microorganisms.
Casadevall and Pirofski (1999)	A microbe capable of causing host damage; the definition can encompass classical pathogens and opportunistic pathogens; host damage can result from either direct microbial action or the host immune response.

Table 2: Alternative definitions of the term pathogen.

In the late 1850s, the revolutionary work of Louis Pasteur further contributed to the body of evidence for germ theory as he determined the role of bacteria in causing diseases. Robert Koch identified the bacterium that causes tuberculosis, *Mycobacterium tuberculosis* (Koch, 1882). He also introduced four criteria used to demonstrate that the relationship between a microorganism and a disease is causal; these are known as Koch’s Postulates (Koch, 1884). The first virus isolated was the Tobacco Mosaic virus in 1892 by the Russian botanist Dmitri Ivanoski, but was not recognized as a “virus” until several years later after further investigations by Martinus Beijerinck in 1898 (Scolthof *et al.*, 1999). Critically, Beijerinck’s studies proved that microorganisms include the non-cellular forms we now recognize as viruses.

The word *pathogen* was first used in the 19th century, following the wide acceptance of the germ theory of disease (Casadevall and Pirofski, 2014). The definition of a *pathogen*, and an understanding of its true nature, remained unresolved for some time. The modern definition of a pathogen most often used is a microorganism that causes, or can cause disease (Pirofski and Casadevall, 2012). This definition, however, is situated within a medical framework, rather than an evolutionary one. This evokes a fundamental question of the nature of pathogens: are there inherent differences between pathogenic and non-pathogenic species? Many of the first described pathogenic microbes were encapsulated or toxigenic bacteria, bolstering the idea that pathogens were distinct lineages of microorganisms.

In the mid-20th century, the argument that pathogens were unique lineages of organisms began to disintegrate, and pathogenic and non-pathogenic microorganisms presented overlapping characteristics. Research showed that microbes could exist in pathogenic and non-pathogenic states by, for example, attenuation in the laboratory. Medical developments such as widely used broad-spectrum antimicrobial agents, immunosuppressive therapies, and newer types of surgery altered host–microbe interactions. These altered dynamics led to an important insight: microbe species that were first considered non-pathogenic could become, in fact, pathogenic. One example is *Candida albicans*, a yeast living in the gastrointestinal tract and the genitourinary tract (Singh *et al.*, 2014). In healthy hosts, *C. albicans* is the commensal yeast that is harmless to the host and benefits from a stable habitat of the host body. Under specific circumstances, such as when the host develops immune disorders (such as AIDS) or following a course of antibiotic treatment, the yeast population can proliferate, becoming overabundant and causing candidiasis. Pathogenicity is therefore not only a microbial trait but the outcome of host–microbe interaction and how the immune system reacts to this interaction. As a result of this, some researchers have argued that the term “pathogen” should be ditched altogether in the medical field (Casadevall and Pirofski, 2014).

Reshaping our understanding

Parasites and pathogens are frequently understood or approached from a non-neutral or partial perspective. This taints our understanding of them as inherently negative which can erode scientific efficacy. Because of our natural inclination to think of ourselves as healthy because we are parasite-free, we project that same idea onto other organisms. A parasite going extinct will often elicit the response “Good riddance!”, even among biologists (Windsor, 1995). This instinct has real and material effects: as parasites are thought of as always harmful, many animals in conservation programs are rid of parasites, which can make them go extinct. For example, the critically endangered Californian condor (*Gymnogyps californianus*) was kept in zoos as part of a breeding program, where the birds were treated with a pesticide to get rid of their lice. This treatment killed the last remaining host-specific Californian condor lice (*Colpocephalum californici*), a form of the paradoxically named conservation-induced extinction (Rózsa and Vas, 2015). While the decision to eliminate the lice for the benefit of the condor has broad appeal, it is important to admit that this is an aesthetic and hierarchical valuation rather than a scientific one. In conservation, parasites tend to be valued less and receive less funding than their host, even though parasites are the most threatened mode of life (Lafferty, 2012). Only recently have parasite conservation programs been put into practice, and it is still considered to be a major oversight in conservation biology (Carlson *et al.*, 2020).

This leads to a different issue faced by parasites: co-extinction. A single species going extinct will usually have cascading effects. The species’ parasites (and commensals and mutualists) risk going extinct with their host, as they are dependent on it to survive. This is especially true of obligate parasites and parasites, which are very host-specific (Dunn *et al.*, 2009). Documentation on co-extinction has historically been lacking, due to incomplete taxonomy and a lack of experiments (Colwell *et al.*, 2012). Models suggest as many as 30% of parasitic worms may go extinct by 2070 (Carlson *et al.*, 2017). Parasites are often not even considered in biodiversity surveys, both due to the lack of knowledge and because of the fear of introducing host species to new parasites. More recently there have been calls to include parasites in conservation strategies (Jørgensen, 2015). Parasites are in themselves a native part of biodiversity and can constitute up to 75% of an ecosystem’s resource-consumer webs (Dougherty *et al.*, 2015). Having rich parasite biodiversity could be considered a good measure of ecological health (Colwell *et al.*, 2012).

Adding to the challenge of understanding parasitology, parasites can be difficult to classify and are frequently confused with mutualists or commensals. This is made even more complicated by the multi-modal nature of some species interactions. For example, Caribbean cleaning gobies (*Elacatinus evelynae*) cleaning longfin damselfish (*Stegastes diencaeus*) switch their interactions between mutualistic, neutral, or parasitic depending on the number of ectoparasites present for cleaning on the damselfish (Cheney and Côté, 2005). Similarly, a recent study on arbuscular mycorrhizal fungal communities of Joshua trees (*Yucca brevifolia*) showed a spectrum of fungal interaction modes—from mutualism to parasitism—correlated with both elevational gradient and host plant developmental age (Harrower and Gilbert, 2021). We also take note of the example of brachiopod annelids that graze on the exoskeletons of freshwater crayfish (*Cambaroides similis*). This grazing has been reported as anywhere from minority parasitic to mutualistic with experiments demonstrating that the nature of this interaction is impacted by environmental conditions (Lee *et al.*, 2009; Skeleton *et al.*, 2013).

Scientists are routinely confronted with the pliable, shifting, and sometimes contradictory webs of ecology. Likewise, the field of microbiology has substantially altered perceptions of individualism in nature by revealing the staggering diversity of microbes living within and amongst multicellular organisms. Although it is quite practical to recognize individual organisms or distinct taxa in science, it is also useful to understand organisms as embedded in biological interdependencies. This phenomenon is captured by the holobiont concept (Margulis, 1991) or hologenome concept (Jefferson, 1994) which emphasizes that the biological characteristics of an organism are most legible when understood as a collection of multispecies interactions over evolutionary time. Microbiologists continue to illuminate the blurred limits of an individual species (e.g., how would the human body function without our microbiota?); this framework also is useful for recasting our understanding of parasitism and pathology.

Similarly, it is most scientifically accurate to emphasize that the impact a pathogen has on its host is the outcome of the evolutionary interaction between both. For example, if the host has a good chance of transmitting the pathogen to other hosts, then a phenotype that includes high reproduction and high infectivity (and usually also high virulence) could be beneficial for the pathogen. If, however, the host does not come into contact with many other hosts, then a more benign character of the pathogen could be an evolutionarily beneficial phenotype for the pathogen. In other words, a pathogen is as much a reflection of its own DNA and phenotype as it is the DNA and phenotype of its host. Hegner *et al.* (1938) argue that “the principles that govern the structure, life cycles, habitats and activities of free-living and parasitic animals are really the same.” Indeed, it is increasingly apparent that these definitions are contextual, and depend greatly on the perceived value of the organisms in question.

Parasitic and pathogenic fungi

Sometimes species are assumed to be parasites without evidence, and sometimes language originating from parasitological or pathogenic biology is incorrectly applied to other forms of symbiosis. For example, throughout foundational literature on endophytic and mycorrhizal fungi, terminology such as “infect” is widely used to describe the interaction (Newman, 1988; Arnold *et al.*, 2003). This term is used even when the fungi in question are demonstrably beneficial to the host plant, which belies a fundamental perception of fungi as being pathogenic or at least dubious (Kaishian and Djoulakian, 2020). Because fungi are also typically excluded from conservation efforts and biodiversity monitoring programs (Fiesler and Drake, 2016; Haelewaters *et al.*, 2024), fungal parasites are doubly at risk of being overlooked. Laboulbeniales, for example, are obligatorily associated with various arthropods (Weir and Hammond, 1997; Haelewaters *et al.*, 2021), but the nature of their characterization has been debated. Are they parasites or rather commensals? The answer may be that Laboulbeniales occupy an overlapping range of both on the spectrum of symbiosis. Based on micro-computed tomography imaging, Reboleira *et al.* (2021) concluded that some species of Laboulbeniales are “ectobionts,” whereas others are “ectoparasites.” However, Konrad *et al.* (2015) also found some evidence for these fungi to provide benefits to their host—in their protection against infection by entomopathogenic fungi. While the limits of the continuum that Laboulbeniales occupy on the symbiosis spectrum are unclear, we know that they are not pathogens, despite having been labeled as such (e.g., Espadaler *et al.*, 2011).

Some studies regarding invertebrate–fungal interactions have used the terms parasite and pathogen interchangeably which adds to the confusion when it comes to definitions (Meyling and Hajek, 2010; Kaya and Vega, 2012). The most widely adopted definitions of these terms in the field of invertebrate pathology within the context of biological control remains those of Onstad *et al.* (2006). They define a parasite as “*an organism that lives at the expense of its host, obtains nutrients from the living substance of the latter, deprives it of useful substance, or exerts other harmful influence upon the host.*” In this sense, a parasite weakens the host immune system, making the host more vulnerable to foreign infectious microorganisms (**Fig. 5**). Therefore, if death of the infected occurs, it does as a direct result of foreign organisms and not of the parasite itself. In epidemiological and ecological studies, the term parasite is usually categorized into two groups: microparasite and macroparasite. The latter one, considered a true parasite, is intensity-dependent meaning that its impact on the host is directly correlated with an increase in the number of infection events (Lafferty *et al.*, 2008; Vega *et al.*, 2012). In contrast, microparasites are analogous to pathogens in that they are intensity-independent—a single infection unit leads to an increase in the number of infectious fungal propagules on the host that further weakens the host or leads to disease (Anderson and May, 1981; Lafferty *et al.*, 2008; Vega *et al.*, 2012).

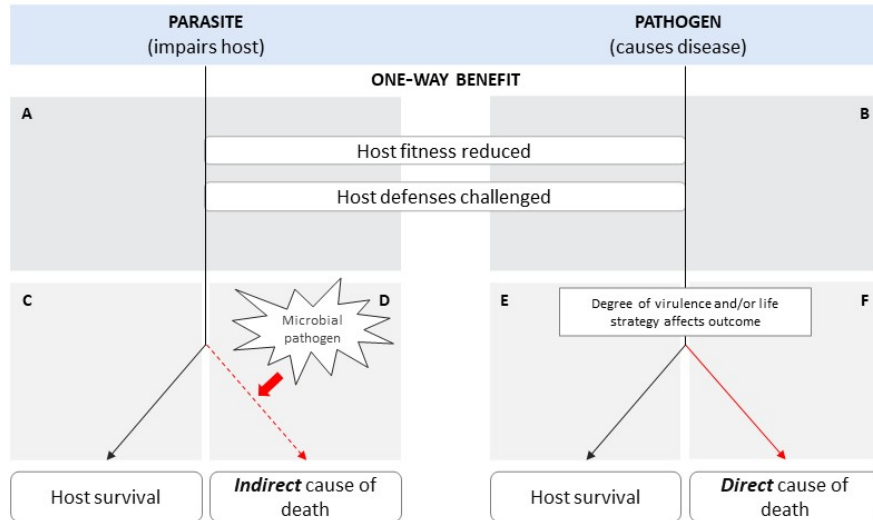


Figure 5: Comparative outcomes of parasite and pathogen infections. A, B. Host fitness is reduced and the host immune system is challenged. C, E. The immune system overcomes infection, and the host survives. D. The host, which has become more susceptible to infection because of a weakened immune system, is ultimately killed by a virulent or an opportunistic microbial pathogen. F. A high degree of virulence and host specificity leads to death of the host. Note that the terms parasite and pathogen are used interchangeably in epidemiological and ecological studies.

Onstad *et al.* (2006) define a pathogen as “a microorganism capable of producing disease under normal conditions of host resistance and rarely living in close association with the host without producing disease.” In mycology, the term “entomopathogenic fungus” (from Greek, *entomon* = insect, *pathos* = suffering, and *gennaein* = to produce) is used to describe a fungus that as part of its life cycle causes disease of a host insect. Consequently, if death of the infected host occurs, it does as a direct result of the disease caused by the pathogen (Fig. 5). This is contrary to infection by a parasite. Entomopathogenic fungi typically kill their host and go on to produce infective fungal spores *on the host itself*— *these new spores then* subsequently infect a new host. In this way the pathogen ensures its own propagation and dissemination. There are exceptions: fungi in the genus *Strongwellsea* represent an interesting outlier among entomopathogenic fungi. These are fly specialists and do not need to kill their host prior to spore dispersal. *Strongwellsea* fungi instead form an abdominal hole in the living fly host through which spores are actively discharged (Eilenberg, 2002; Eilenberg *et al.*, 2020, 2022).

Death or survival of an insect host following infection by a pathogen is strongly correlated with pathogen features – host specificity, degree of virulence, life strategy – in combination with the host’s immune response to infection. Knowledge related to host specificity (i.e., generalist versus specialist) and life strategy (i.e., obligatory versus facultative) of entomopathogenic fungi is of utmost interest for ecological studies. Host specificity of entomopathogenic fungi ranges from specialists with extreme to moderate host specialization to generalists encompassing a broad host range. Life strategy is intrinsically linked to host specialization. Obligate pathogens are strictly dependent on their host for nutrients and for survival; this entails adaptations and counteradaptations from pathogen and host. Therefore, obligate pathogens have high host specificity. An extreme example is *Entomophthora muscae* sensu stricto of which certain isolates infect only a single fly species (Jensen *et al.*, 2021). On the other end of the spectrum are facultative pathogens, those that do not need the host for survival and can obtain nutrients as saprotrophs from other sources. *Beauveria bassiana* is an example of a facultative pathogen. It infects hosts in multiple different orders and is able to persist in living plant tissues and soil (Meyling and Eilenberg, 2006; Meyling *et al.*, 2009).

Epilogue

Scientific breakthroughs have challenged our understanding of parasites and pathogens throughout history, repeatedly changing their definitions accordingly. We acknowledge that the line between the definitions of parasites and pathogens is not always clear. Microbial pathogens that are biotrophic may be similar to parasites in lifestyle—deriving a benefit from their host without killing it. In this case, one might wonder about the difference between a multicellular parasite and a multicellular microbial pathogen. Rapid developments in the field of cell biology, molecular biology, and bioinformatics will continue to increase our knowledge about parasite–host and pathogen–host interactions. We would not be surprised if the definitions of parasites and pathogens continue to change into the future, including new interactions and excluding old ones.

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