MICROBIOLOGY

Interacting Parasites

Parasites interact in complex ways in the voles they infect.

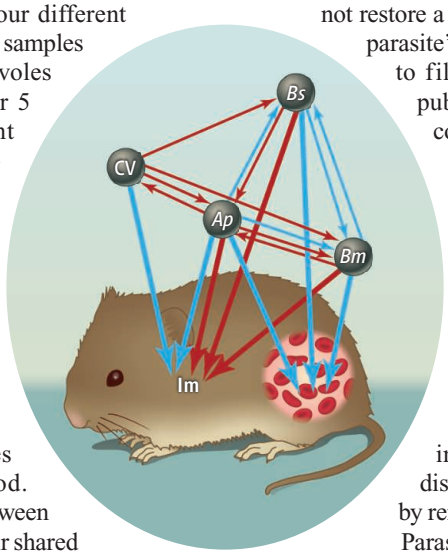
Kevin D. Lafferty

Parasitism is the most popular life-style on Earth, and many vertebrates host more than one kind of parasite at a time. A common assumption is that parasite species rarely interact, because they often exploit different tissues in a host, and this use of discrete resources limits competition (*1*). On page 243 of this issue, however, Telfer *et al*. (*2*) provide a convincing case of a highly interactive parasite community in voles, and show how infection with one parasite can affect susceptibility to others. If some human parasites are equally interactive, our current, disease-by-disease approach to modeling and treating infectious diseases is inadequate (*3*).

Telfer *et al*.'s study—which involved tracking infections of four different parasites by taking blood samples from nearly 6000 wild voles (*Microtus agrestis*) over 5 years—helps highlight our growing understanding of how parasites can interact in complex ways (see the figure). What are some of the take-home messages?

Parasites are consumers and can compete for resources. In Telfer *et al*.'s voles, for instance, some parasites may compete for blood. Because competition between parasites increases as their shared resource becomes limited (*4*), parasites that grow or reproduce substantially within the host are more likely to compete (*5*). Early experiments demonstrated that one kind of intestinal parasite, acanthocephalan worms, displaced tapeworms from the best sites within the intestine and competed for food (*6*). Studies have also indicated that the malaria parasite competes with parasitic worms for red blood cells, a finding with important implications for human health (*7*).

Parasites also apparently engage in competition through a phenomenon called cross immunity (*3*). Immune system cells, such as memory T cells, produced in response to one parasite can cross-react with antigens from similar parasite species (*8*). For this reason, infection with one species of human schistosome (a trematode worm) can protect against new infections by other schistosome species (*9*). Cross immunity to a wider range of parasites can arise after the immune system's generation of a network of regulatory cells and cytokines in response to infection (*8*). In Telfer *et al*.'s study, cross immunity could explain why voles infected by the protozoan *Babesia microti* show reduced susceptibility to *Bartonella* bacteria, but the result also could indicate competition for blood cells. Whatever the mechanism, targeting treatment of one parasite in a mixed infection might not restore a patient to health if the parasite's competitor responds to fill the void. Similarly, public health campaigns could have net negative consequences if they inadvertently promote disease-causing parasites by removing competitors.



Vole parasite interactions. Four pathogenss—cowpox virus (CV), the protozoan *B. microti* (*Bm*), *and two bacteria, A. phagocytophilum* (*Ap*) *and Bartonella* spp. (*Bs*)—can have positive effects (red lines) and negative effects (blue lines) on each other (*2*). Thick lines are proposed direct effects on the host vole (*M. agrestis*) and thin lines are proposed indirect effects among parasites. Im represents the immune system, and the inset circle represents a limited pool of red blood cells.

Parasites sometimes facilitate each other. Co-infections with dissimilar parasites can spread the immune system thin (*3*). Shedding of the severe acute respiratory syndrome (SARS) virus increases, for instance, if a person has a concurrent pulmonary infection; for this reason, a few co-infected persons became super spreaders in the SARS epidemic (*10*). Parasites can also suppress the immune system, opening the door for others. Most notably, infection with HIV facilitates opportunistic bacterial, fungal, protozoal, and viral pathogens (*11*). Indeed, HIV's ability to suppress the immune system is the principal cause of its devastating morbidity and mortality in untreated cases. As Telfer *et al*. mention, HIV also increases the potential for tuberculosis to spread to the general population (*12*). Parasitic worms can also suppress the inflammation response of the immune system, making it easier for certain protozoan parasites to succeed (*7*). In voles, cowpox appears to temporarily impair the immune system and increase their susceptibility to other parasites (*2*). If it is easier to control a facilitating parasite than a disease agent it facilitates, then targeting the facilitator could be an efficient way to manage epidemics.

When do interactions matter? The answer can depend on the strength of the interactions, the prevalence of potential interacting species, and various factors that tend to intensify interactions or isolate species from one another in space and time (*13*). The finding that infection with one parasite greatly increases susceptibility to infection by a second parasite is meaningful only to the extent that the host is exposed to both parasites in nature. Voles, for instance, are much less frequently exposed to *Anaplasma phagocytophilum* bacteria than they are to other parasites, reducing the influence of this particular parasite on community dynamics, despite its potentially strong effects on the other species. To isolate how one parasite affected susceptibility to other parasites, Telfer *et al*. used statistical techniques to control for confounding factors. This was essential to quantify per-capita susceptibility, but the approach also obscured factors that might affect the frequency of interactions at the host population level. Now that they have illustrated the strength of interactions, Telfer *et al*. have the opportunity to consider whether environmental, spatial, temporal, or demographic factors increase or decrease the frequency of coexposure to parasites.

Voles have more to worry about than the network of four pathogens studied by Telfer *et al*. What would infection patterns look like if the several parasitic worms that infect voles (*14*) were included? Worms can interact strongly with viruses, bacteria, and protozoa (*7*). How might immune-modulated effects and competition for resources interact? In

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natural ecosystems, strong predation pressure can reduce the abundance of competitors so that resources are no longer limiting (*15*). This basic premise of community ecology should apply to parasite communities as well, where the host immune system can act as a predator on parasites. An impaired immune system (like release from predation in free-living communities) should set the stage for more intense competition among parasites. This is a key difference between free-living systems and parasite communities, because prey are less likely to impair predator populations. Even more challenging to predict are the myriad indirect interactions within a community of parasites. If parasites can affect each other indirectly through long causal chains, the study of parasite communities could benefit from modern approaches to dealing with complexity, such as network theory and structural equation modeling.

A further challenge for parasite ecologists will be to examine how effects on host susceptibility translate into effects on host and parasite population dynamics (*3*). In addition to affecting susceptibility, parasites can interact through their negative effects on host survivorship and population densities, leading to the potential for complex feedbacks among pathogens at the population level. In addition, interactions among parasites, and between parasites and the immune system, have the potential to alter the course of virulence evolution in parasites (*16*).

There is enough evidence that human parasites interact to motivate systematic investigations of parasite communities in human populations. Telfer *et al*. provide an example of how, through collecting infection data over time, one could quantify the importance of parasite interactions in humans. With such information, we would know better when to stop treating and managing parasites one species at a time.

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CHEMISTRY

Inorganic Nanoparticles as Protein Mimics

Inorganic nanoparticles coated with organic films can display surface chemistries that allow them to function like globular proteins.

Nicholas A. Kotov

Water-soluble inorganic nanoparticles (NPs) and globular proteins (GPs) might seem "as different as chalk and cheese," especially in the interior. The chemical structure of GPs is usually exact and well-defined, whereas NPs are almost always formed as a mixture of sizes and variation of shapes. The complexity and dynamism of three-dimensional atomic organization inside the protein globules and related functionalities are not present in the impenetrable crystalline cores of NPs. However, NPs and GPs do reveal similarities in overall size, charge, and shape, and the exterior surfaces of NPs can be coated with organic functional groups similar to those exposed by GPs, which suggest that NPs could function as protein mimics. This option is attractive because NPs are usually cheaper and more stable than proteins, but can they actually display the same functionalities and achieve enough specificity to replace proteins?

The majority of preparation schemes of water-soluble NPs use thin coatings of small organic molecules, or stabilizers, with a variety of functional groups and some degree of anisotropy (*1*). The methods for separating, purifying, and solubilizing NPs and GPs are similar (*2*–*4*). Typical sizes of NPs and GPs are comparable to nanometer-scale features of cellular membranes, such as ion channels (*5*). The interactions of water-soluble NPs and GPs with the environment and other soluble molecules are virtually identical and depend on the same media parameters. For example, surface charges of both NPs and GPs depend on pH and ionic strength and can influence their binding interactions to cellular membranes (*5*). If needed, the NP coatings may also

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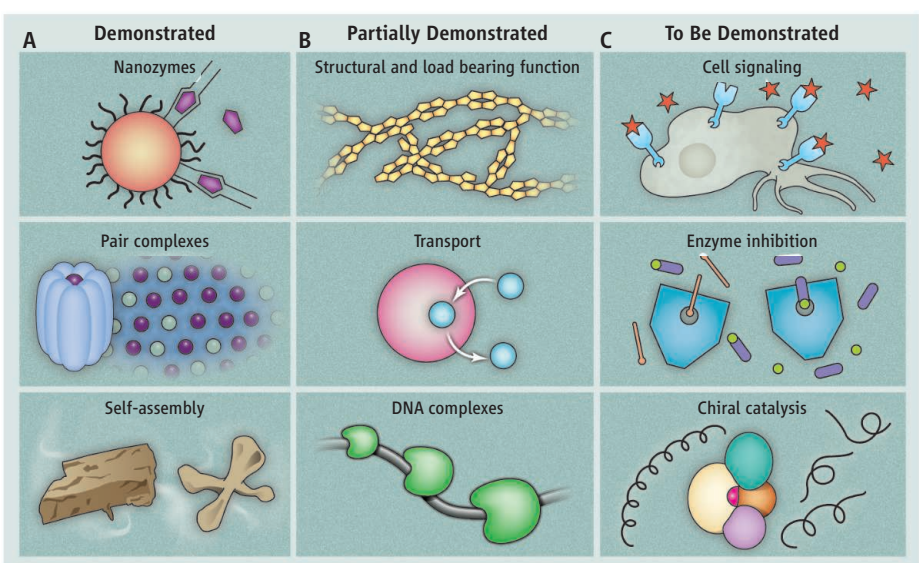

Nanoparticles vie for protein jobs. Examples of (**A**) demonstrated, (**B**) partially demonstrated, and (**C**) potential functional similarities between water-soluble nanoparticles and globular proteins.

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