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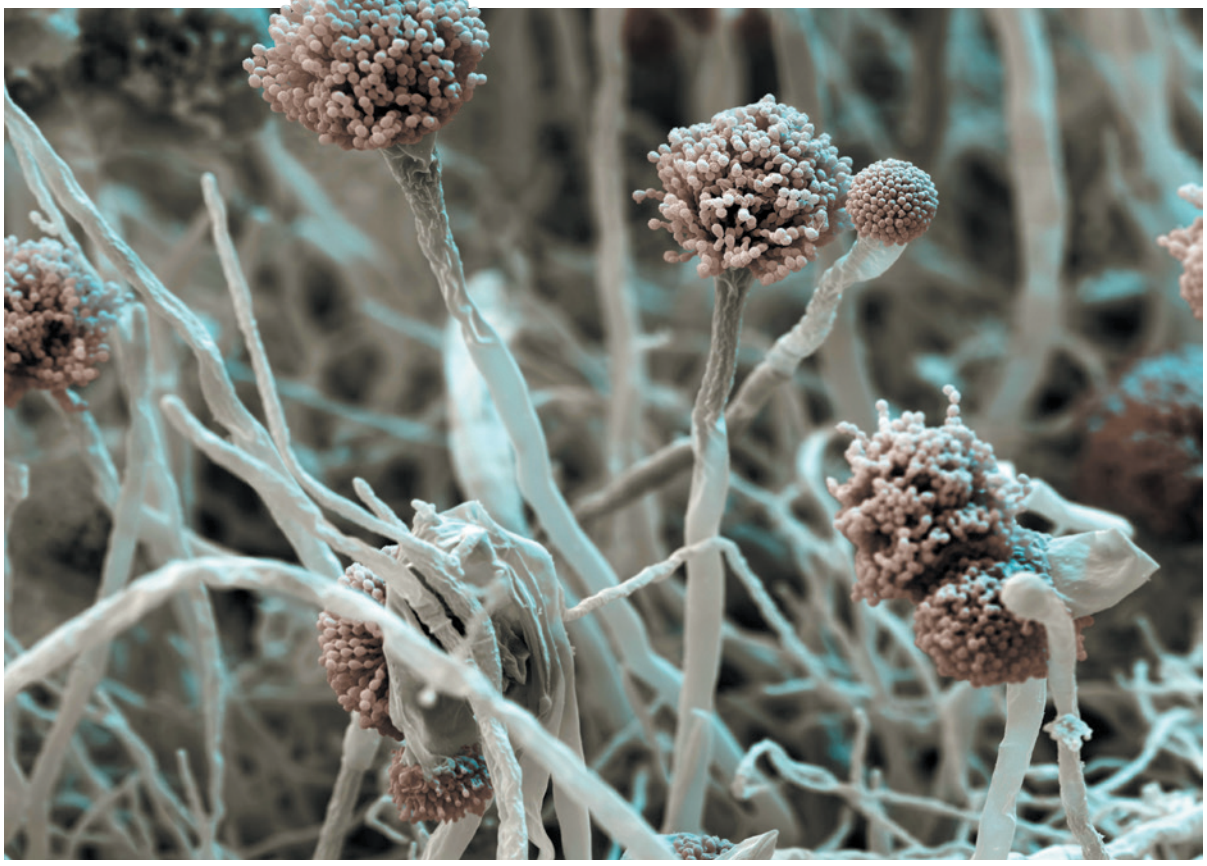

EYE OF SCIENCE/SPL

The often harmless fungus *Aspergillus fumigatus* can cause severe pulmonary disease in people with leukaemia.

Ditch the term pathogen

Disease is as much about the host as it is the infectious agent — the focus on microbes is hindering research into treatments, say **Arturo Casadevall** and **Liise-anne Pirofski**.

The term pathogen started to be used in the late 1880s to mean a microbe that can cause disease. Ever since, scientists have been searching for properties in bacteria, fungi, viruses and parasites that account for their ability to make us ill. Some seminal discoveries have resulted — such as the roles of various bacterial and fungal toxins in disease. Indeed, our oldest and most reliable vaccines, such as those for diphtheria and tetanus, work by prompting the body to produce antibodies that neutralize bacterial toxins.

Yet a microbe cannot cause disease without a host. What actually kills people with diphtheria, for example, is the strong inflammatory response that the diphtheria toxin triggers, including a thick grey coating on the throat that can obstruct breathing. Likewise, it is the massive activation of white blood cells triggered by certain strains of *Staphylococcus* and *Streptococcus* bacteria that can lead to toxic-shock syndrome.

Disease is one of several possible outcomes of an interaction between a host and a microbe. It sounds obvious spelled out in this way. But the issue here is more than just semantics: the use of the term pathogen sustains an unhelpful focus among researchers and clinicians on microbes that could be hindering the discovery of treatments. In the current Ebola epidemic in West Africa, for instance, much attention has been focused on the ill and the dead, even though crucial clues to curbing the outbreak may ▶

be found in those who remain healthy despite being exposed to the virus.

Instead of focusing on what microbes do or do not do[1], researchers should ask whether an interaction between a host and a microbe damages the host, and if so, how. This approach will require different tools and potentially more alliances between microbiologists and immunologists.

CONTEXT IS EVERYTHING

In the decades after the word pathogen was coined, it became clear that many 'non-pathogens' can be harmful in some people. Until the 1950s, for example, coagulase-negative staphylococci (part of the normal flora of human skin) and *Candida albicans* (usually present in the vagina, mouth and gut, and on the skin) were rarely associated with disease. Infections caused by these microbes then became common with the use of intravenous catheters, which open a channel between the skin and the blood, and treatments that suppress immunity, such as chemotherapy.

"Much of the research on infectious diseases continues to be dominated by reductionist approaches."

This prompted microbiologists to use qualifiers, mostly from the 1960s onwards, to define microbes according to their state in the host organism. For instance, 'commensal' was used to describe microbes that live on or in hosts without causing harm, such as *Escherichia coli*, one of the many species present in the human gut; 'colonizer' referred to organisms commonly found in the human body but able to cause disease, such as *Staphylococcus*; 'saprophyte' described organisms associated with dead plant material, including the fungus *Aspergillus fumigatus*.

But even these qualifiers proved inadequate. Microbes and hosts are variable and unpredictable. For instance, *A. fumigatus* can cause severe pulmonary disease in people with leukaemia; some strains of *E. coli* can cause diarrhoea and vomiting, and in one out of three people, *Staphylococcus aureus* behaves more like a commensal, inhabiting nasal cavities without causing harm.

During the 1970s, biologists began to try to identify microbial genes that confer pathogenicity. Researchers deleted or inactivated genes in search of those encoding 'virulence factors', molecules thought to enable a microbe to invade and inhabit a host and cause disease. This hunt for microbial genes or mutations associated with disease continues to this day. For example, researchers are applying genomics to try to discern signatures of virulence among *S. aureus*, *Haemophilus influenzae* and *Enterococcus faecium* strains, to name a few[2–4].

The approach has worked extremely well for some bacteria. For example, knocking out the toxin and capsule genes of *Bacillus anthracis* rendered the bacterium less virulent, and so suitable for use in a vaccine against anthrax. It has been less successful with other microbes, such as types of fungus. More than two decades of research have been devoted to trying to find microbial factors that enable *C. albicans* and *A. fumigatus* to cause disease. In neither case does a single classical virulence factor seem to have a big effect on pathogenicity.

VACCINE CHALLENGES

Work on vaccines has provided further indications of there being flaws in the idea that discrete factors, akin to toxins, enable all microbes to cause disease.

Most vaccine research has focused on identifying and neutralizing microbes' virulence factors. In numerous cases, this tactic has paid off. The vaccines for tetanus and diphtheria work on this basis, and have eliminated two major killers from the Western world. Similarly, a vaccine that makes the polysaccharide capsule of bacteria vulnerable to attack from white blood cells by prompting lymphocytes to produce antibodies against it has virtually eradicated *H. influenzae* type B, a major cause of meningitis before the 1980s. Since 2000, similar vaccines have markedly reduced the incidence of disease caused by *Streptococcus pneumoniae*.

Yet at least for *S. pneumoniae*, the idea that antibodies prevent disease solely by promoting uptake and killing of the microbe by immune cells called phagocytes is too simplistic. The mere presence of antibodies to *S. pneumoniae* in someone's blood, for instance, does not reliably indicate that the person will be protected from pneumonia. What is more, many of the ongoing attempts to develop new vaccines by identifying and targeting virulence factors have so far proved fruitless. Despite decades of searching, no classical virulence factor suitable for vaccine development has been identified for the tuberculosis bacillus or malaria parasite.

In some cases, efforts aiming to neutralize virulence factors may even have uncovered ways to exacerbate disease. Pulmonary tuberculosis occurs in less than 10% of people infected with *Mycobacterium tuberculosis*. In these people, an over-exuberant inflammatory response destroys lung tissue. Thus, vaccines against tuberculosis that are designed to enhance the immune response might not work.

This could explain why in the 1890s, when microbiologist Robert Koch injected people who had tuberculosis with an extract that he had produced from culturing the bacteria in the laboratory, many of them died. It could also explain why certain vaccines produced in the past century, for instance for the respiratory syncytial virus, failed to prevent disease.

CHANGING DYNAMICS

The term pathogen is unlikely to go away. But those who study infectious diseases need to own up to its limitations.

Researchers probing the human microbiome (the community of microorganisms that live in and on our bodies) using genomics are being forced to recognize that myriad factors and interactions shape its composition. It varies in different people, at different times in development and in association with disease.

Yet much of the research on infectious diseases continues to be dominated by reductionist approaches; one variable is altered while all others are assumed to hold constant. Microbiologists tend to view the microbe as the key variable in disease and treat the host as a constant. Immunologists generally see the microbe as a constant and the host response as the variable (for instance, immunologists frequently inject microbes into normal and genetically manipulated laboratory animals, to assess the factors that shape the host response)[5]. These two groups go to different conferences, read and publish in different journals, and receive funds from different granting panels.

What is needed is the simultaneous analysis of microbial and host variables using new analytical tools. Damage to the host is a measurable parameter that can result from the microbe, the host's response, or both, and as such, it shifts the focus onto the host–microbe interaction[6].

New tools are needed to measure the spectrum of inflammatory, biochemical and other forms of damage resulting from the interaction between hosts and microbes. The discovery and development of these tools must be driven by new sessions at conferences, special issues of journals and dedicated funding streams. We think that such a shift in approach would uncover all sorts of possibilities for preventing infectious diseases. ■

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1. Pirofski, L. A. & Casadevall, A. *BMC Biol.* **10,** 6 (2012).
2. Howden, B. P. *et al. mBio* **4,** e00412-13 (2013).
3. De Chiara, M. *et al. Proc. Natl Acad. Sci. USA* **111,** 5439–5444 (2014).
4. Young, B. C. *et al. Proc. Natl Acad. Sci. USA* **109,** 4550–4555 (2012).
5. Biron, C. A. & Casadevall, A. *mBio* **1,** e00260-10 (2010).
6. Casadevall, A. & Pirofski, L. A. *Nature Microbiol. Rev.* **1,** 17–24 (2003).