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*Annual Review of Microbiology*

The Microbe, the Infection  
Enigma, and the Host

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**Keywords**

microbial theory, host theory, genetic theory, inborn errors of immunity, anticytokine autoantibodies, infectious diseases

**Abstract**

Human infectious diseases are unique in that the discovery of their environmental trigger, the microbe, was sufficient to drive the development of extraordinarily effective principles and tools for their prevention or cure. This unique medical prowess has outpaced, and perhaps even hindered, the development of scientific progress of equal magnitude in the biological understanding of infectious diseases. Indeed, the hope kindled by the germ theory of disease was rapidly subdued by the infection enigma, in need of a host solution, when it was realized that most individuals infected with most infectious agents continue to do well. The root causes of disease and death in the unhappy few remained unclear. While canonical approaches in vitro (cellular microbiology), in vivo (animal models), and in natura (clinical studies) analyzed the consequences of infection with a microbe, considered to be the cause of disease, in cells, tissues, or organisms seen as a uniform host, alternative approaches searched for preexisting causes of disease, particularly human genetic and immunological determinants in populations of diverse individuals infected with a trigger microbe.

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## 1. INTRODUCTION

We refer to the immense interindividual clinical variability in the course of any infection, ranging from silent infection to lethal disease, as the infection enigma. It is particularly striking that clinical disease, and death from disease in particular, is the exception and not the rule among infected individuals (27, 29). Even for the small number of infections for which this is not yet the case—those caused by the most virulent microbes of the day (e.g., HIV, Ebola virus)—it will probably end up being so in the future, once natural selection has operated on susceptibility to these infections, as initially suggested by J.B.S. Haldane (60). Currently, no more than a dozen of the approximately 3,000 known human infections (if microbial species are considered or >700 if genera are considered; **Figure 1a,b**) (12, 45, 49, 89) can kill more than 10% of unvaccinated infected people in the absence of medical care. Most of the approximately 3,000 infections currently known can kill only less than 1% of infected individuals in the absence of medical care (**Figure 1c**). In this natural setting, most of these microbes would be predicted to lose virulence in humans progressively, if not because of their own evolution, then at least because of our own. Unchecked HIV infection would have selected C-C chemokine receptor 5 (CCR5)-deficient humans (carrying CD4<sup>+</sup> T cells that cannot be infected with HIV) in Europe in the same way that *Plasmodium vivax* has selected Duffy antigen and receptor for chemokines (DARC)-deficient humans (carrying Duffy-negative erythrocytes that cannot be infected by *P. vivax*) in Africa (26, 64). Conversely, medical interventions can select drug-resistant microbes, facilitating their spread and thereby making them more virulent in patients receiving medical care (7, 113).

For any given microbe, the proportion of infected individuals with life-threatening disease also varies considerably between age groups. One remarkable feature of endemic infections is the classic U-shaped curve of the age-dependent mortality rates, with children and the elderly most vulnerable, and the rarer L-shaped curve with no increased risk of death in the elderly (1, 3). Less is known about emerging infections. The mortality rates of the Spanish influenza pandemic of 1918 followed a W-shaped curve (2). By contrast, COVID-19 mortality rates doubled every 5 years of age from childhood onward, with a J-shaped curve (104). The infection enigma can thus be broken down into three facets: (a) Death is a globally rare outcome of infection; (b) the risk of death depends on the microbe; and (c) for any given microbe, the risk of death depends on the age of

### Infection enigma:

the immense interindividual clinical variability observed in the course of any infection, ranging from silent infection to lethal disease

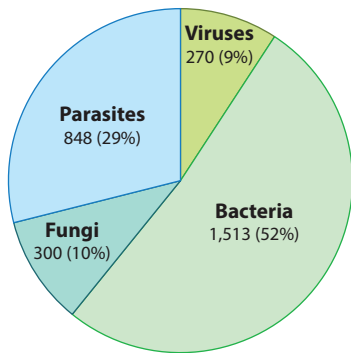
**DARC:** Duffy antigen and receptor for chemokines

the host. A corollary of the infection enigma is that death from microbial disease is not caused by microbes any more than death from peanut allergy is caused by peanuts or, using an example that brings human genetics into the frame, any more than death from phenylketonuria is caused by phenylalanine (91, 107). The trigger (the microbe) is environmental and of course required for infection, but the cause of disease lies in the host, the individual human, whose vulnerability preexists infection and mechanistically underlies disease, which is conditional on infection (24). The root cause of disease must be present before the disease and must mechanistically drive the disease. The microbial trigger is originally external in that regard, even though it can replicate within and interfere with the host. The microbe can also evolve within the host by natural selection, albeit with greater long-term consequences than short-term consequences, more at the population level than at the individual level. Death from infection thus logically attests to an immunodeficiency, which may be overt or covert and inherited or acquired. We invite readers to adopt this perspective, if only while reading this article.

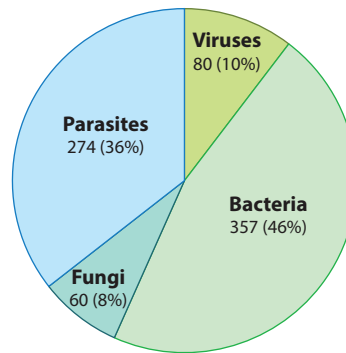
Following the establishment of the germ theory of disease by Louis Pasteur between 1865 and 1875, general principles for preventing and curing infectious diseases were rapidly and firmly established (26). Robert Koch's postulates were excessively stringent, and while his radical version of

**Germ theory of disease:** the proven notion that infection with microbes is necessary for the development of infectious diseases

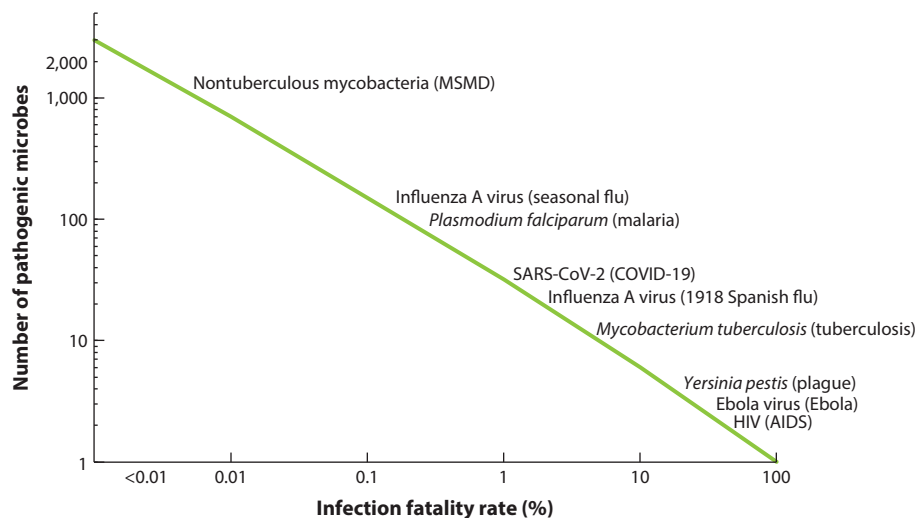
**a** 2,931 human pathogenic microbial species



**b** 771 human pathogenic microbial genera



**c**



(Caption appears on following page)

**Figure 1** (Figure appears on preceding page)

Estimated numbers of microbial species (*a*) and genera (*b*) that can infect and harm humans, regardless of the proportion of infected individuals that actually become sick. Numbers for virus species were obtained from Reference 49 and numbers for virus genera were estimated from References 99 and 123, numbers for bacteria species and genera were obtained from Reference 12, numbers for fungal species were obtained from Reference 45 and numbers for fungal genera were estimated from References 75 and 125, and numbers for parasite species and genera were obtained from Reference 89. (*c*) A putatively linear relationship between this number of human pathogenic microbes (*y*-axis) and the infection fatality ratio (IFR) (*x*-axis). The IFR is an estimate of the proportion of deaths among infected people in the absence of treatment. Infected individuals include not only diagnosed patients (cases) with asymptomatic or symptomatic infection but also undiagnosed individuals, based on retrospective evidence (serological or otherwise) at the population level. Untreated deaths are the clinical outcome in the absence of medical intervention. The IFR is very difficult to estimate for most infectious diseases, due to both the often unknown proportion of undiagnosed infections and the nature of medical care, which varies greatly according to the period and region considered. The IFR is always lower, and often much lower, than the case fatality rate (CFR), which is the proportion of people diagnosed with a condition who die from it. Based in part on the list of CFRs provided by Reference 147, we estimate that fewer than 10 microbial species have an IFR greater than 10%, and less than 30 have an IFR greater than 1% in the general population in the absence of specific treatment. In this figure, we have extrapolated the data for lower IFRs, assuming a log-linear relationship between the IFR and the number of pathogenic microbes. We used an estimated number of microbial species of 2,931 (see panel *a*), not taking into account the large number of subspecies or strains within each microbial species, as illustrated by a recent seasonal influenza virus and the 1918 pandemic influenza A virus. The figure displays some examples of microbes and their associated diseases.

germ theory facilitated the discovery of new pathogens, it may have slowed down our understanding of infectious diseases (46, 94). Hygiene was widely improved; Joseph Lister (83) pioneered aseptic surgery in 1867, and Pasteur developed the concept of vaccination, which he implemented in 1882 (95). It took a few more decades for Gerhard Domagk (43) to demonstrate the efficacy of sulfamides in 1932, while Oswald T. Avery & René Dubos (9) searched for antibiotics, unearthing several of insufficient power in 1930, and Alexander Fleming (47) discovered powerful antibiotics without realizing it as early as 1928. It is hard to think of any medical progress to date that can match the conquests that followed the publication of the germ theory. These conquests single-handedly account for most of the shift in life expectancy from approximately 25 years in the middle of the nineteenth century to approximately 80 years today (25). The medicine of infectious diseases, in humans as in other multicellular species, is extraordinary, as recently illustrated with the swift development of efficient medicines and vaccines against SARS-CoV-2. However, the science of infectious diseases (i.e., the understanding of their pathogenesis) continues to lag behind, as attested by the infection enigma and its three facets, which until the turn of the twenty-first century remained only marginally clearer than they were at the turn of the twentieth century. Paradoxically, this lag may be a consequence of the unparalleled success of the medicine of infectious diseases. If infectious diseases can be prevented or cured on the basis of solid principles, why do we need to better understand them?

Perhaps the best evidence of the negative impact of medicine on science is the observation that research funding dries up for any infection that has been efficiently prevented or cured. The eradication of smallpox essentially put an end to scientific studies of this disease (97). Similarly, the recent introduction of direct-acting antiviral agents that are effective against hepatitis C virus (HCV) has strongly decreased research efforts in the field of HCV (11). More recently, scientific interest in SARS-CoV-2 lost momentum as soon as RNA vaccines became available. Prevention or cure is even a stated direct aim of most of the research funded in the field of infectious diseases. It is only rarely an indirect aim of such studies, typically in contexts in which basic research might have long-term clinical implications. This extraordinary differential between medical and

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**HCV:**  
hepatitis C virus

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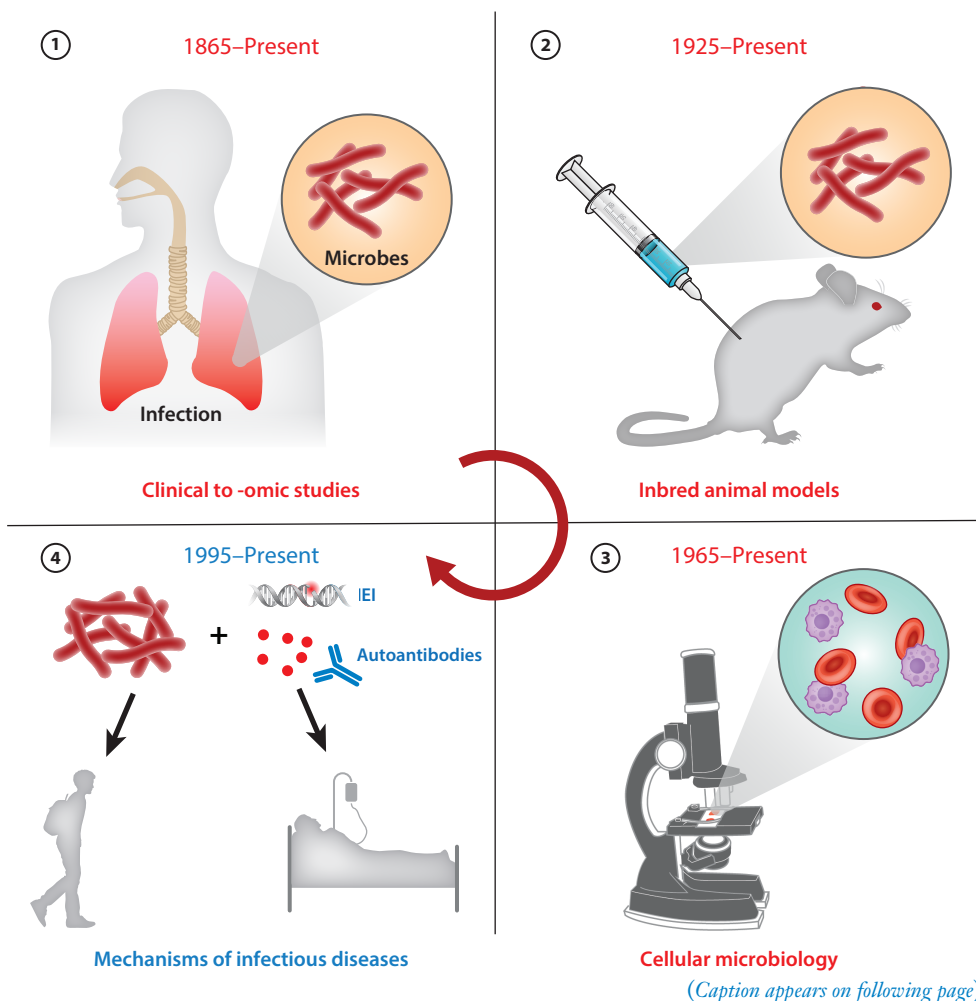
scientific output is probably unique to infectious diseases. Knowledge of their environmental component, the microbe, has been sufficient to permit both vaccination, the known mechanism of which remains paradoxically limited to the requirement of adaptive immunity, and the development of anti-infectious drugs, which selectively or preferentially interfere with the microbial life cycle. The only known radical increase in human longevity, from 25 to 80 years, can be attributed largely to the germ theory (23, 25). Therefore, there has been little need and incentive to decipher the root cause of infectious diseases, beyond the microbial trigger, for the prevention or cure of these diseases or indeed even for their diagnosis or assessment of prognosis.

In our view, this explains why the study of infectious diseases can be historically divided into two broad categories of unequal volume (**Figure 2**): canonical approaches and alternative approaches. Canonical approaches are based on the premise that the microbe is the cause of disease. They involve an in-depth analysis of the consequences of infection in naturally infected individuals, describing the natural course of infection and disease, with the various clinical forms and outcomes. A first type of canonical approach can be used to identify epidemiological risk factors (e.g., age) and biological correlates of severity (e.g., inflammatory markers). A second type of canonical

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**Canonical approaches:** studies of infectious diseases that analyze the consequences of infection with a given microbe considered to be causal for the disease in organisms viewed as uniform hosts

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**Figure 2** (Figure appears on preceding page)

Studies of human infectious diseases have evolved in four major steps. Each step began with the identification of disease-causing microbes and was rooted in concepts proposed no later than the turn of the twentieth century, but the steps have matured into self-autonomous fields over different time periods. (①) The first step began with the detailed clinical and pathological description of diseases in the nineteenth century and has more recently evolved into detailed investigations of patients with various -omics techniques. (②) The second step began at about the same time as the first with the experimental inoculation of an animal with a microbe, initially to test one of Koch's postulates. This step was particularly powerful for studying infectious diseases, especially once inbred animals were generated in the 1920s, as a means of restricting and then analyzing the host component of infection outcome variability. (③) The third step built on microscopic microbiological diagnostic techniques with the development of a new aim from the 1960s onward: to analyze the fate of microbes infecting cells *in vitro* and the fate of the infected cells, defining the field of cellular microbiology at the intersection of cell biology and molecular microbiology. These first three steps are part of the canonical approach, as they study the consequences of infection, which is seen as causal for disease. (④) The fourth, alternative, step is rooted in plant, animal, and human studies of classical genetics from the turn of the twentieth century onward and analyses of the impact of acquired immunodeficiencies from the 1960s onward. It underwent a transition to molecular genetics with the identification of the first inborn errors of immunity (IEIs) underlying an isolated infectious disease from 1996 onward. Since 2004, the discovery of autoimmune phenocopies of inborn errors of cytokines due to autoantibodies against various cytokines has driven further characterization of the human determinants of infectious diseases. Step ④ is characteristic of the alternative approach, as it sees microbial infection as an environmental trigger revealing a preexisting cause of disease and death in the host.

approach can also be conducted in the laboratory by analyzing the consequences of experimental infection in laboratory animal species, typically by comparing a wild-type inbred strain of mice with isogenic animals devoid of specific gene products due to a genetic modification (gene knock-out) or as a result of another method (antibody-mediated depletion). This approach led to the identification of potential mechanisms of immunity to infection by inference from experimental infection in one species (e.g., mouse) to natural infection in another (e.g., human). However, such studies were rarely undertaken with the aim of understanding the interindividual variability of infection in humans. Instead, they typically aim to define a putatively general mechanism of host defense. Finally, a third type of canonical approach involves analyzing the fate of microbes infecting cells *in vitro* and the fate of the infected cells, thereby defining the field of cellular microbiology at the intersection of cell biology and molecular microbiology. This reductionist approach permitted the analysis of the interaction between individual microbes and host cells without the confounding contributions of other cells, tissues, or organs. Studies following these three mainstream approaches can be considered canonical because they did not challenge the notion that the microbe causes disease.

In parallel, an alternative approach has involved testing the hypothesis that deceased infected individuals, unlike individuals silently infected with the same microbe, die because they were deficient in a key component of host defense before they became infected. Microbiologists and immunologists have historically favored canonical approaches, whereas from 1905 onward, this alternative approach became the preserve of primarily geneticists searching for inherited causes of severe infection and initially included both Mendelians (e.g., Archibald Garrod) and biometricians (e.g., Karl Pearson) and their disciples (24, 26, 27). The host genetic approach has followed two parallel paths, as in other fields of genetics, with patient- and family-based searches for rare genetic variants and causal mechanisms on the one hand and population- and ancestry-based searches for common variants and associated risks on the other. The search for monogenic inborn errors of immunity (IEIs) underlying rare or common infectious diseases led to the discovery of common IEIs underlying common infectious diseases (29). The discovery of rare IEIs also led to that of rare or common autoimmune phenocopies underlying rare or common infections. The best examples

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#### Alternative approaches:

studies of infectious diseases that search for causes of infectious diseases present before the infection in populations of diverse individuals infected with a given microbe

**IEI:** inborn error of immunity

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are cytokine-neutralizing autoantibodies, which phenocopy monogenic inborn errors of the corresponding cytokines (34, 114). Acquired immunodeficiencies also contributed to the field from the 1950s onward, with immunosuppressive treatments and HIV infection each having a massive impact. Importantly, acquired immunodeficiencies led some microbiologists and immunologists to join geneticists in their endeavors based on alternative approaches. The alternative approach is noncanonical because it sees the microbe as a trigger and aims to discover and characterize preexisting and underlying root causes of death and detailed mechanisms of disease.

## 2. THE CANONICAL APPROACHES: MICROBIAL INFECTION IS THE CAUSE OF DISEASE

Canonical approaches search for the consequences of infection with a microbe, considered to be the cause of disease, in cells or organisms seen as a uniform host.

### 2.1. Microbiological Studies

The canonical approach in human infectious diseases invariably starts with the search for a causal microbe—a pathogen. Microbiologists are primarily “microbe hunters,” as Paul De Kruif (40) put it. Perhaps the most stringent criteria for identifying pathogens were those defined by Koch in 1882 with his postulates, including the notion that the causal microbe must be found in all patients with the condition studied and not in any healthy individual (95). The simplicity of this notion left an imprint in the minds of many or most of the generations of microbe hunters. However, it rapidly became clear by the turn of the twentieth century not only that several different microbes can underlie the same condition but also that each of these microbes can also be found in many healthy people (103). There is insufficient space to review the epic history of this fruitful hunt for new pathogens (128), which resulted in the identification of approximately 3,000 human pathogens (Figure 1a). Instead, let us consider three emblematic examples of conditions only recently shown to be microbial to illustrate a key point of this article. Whipple’s disease, a rare medical problem first described in 1907, was shown in 2000 to be due to *Tropheryma whipplei*, an abundant saprophyte; however, the ingestion of this saprophyte causes Whipple’s disease in only approximately 1 in 1 million individuals (122). Gastric ulcer, which was a common chronic medical problem in the nineteenth century, has a lifetime prevalence of 5% to 10% and is life-threatening in less than 0.2% of cases (81, 85). It was shown in 1983–1984 that gastric ulcers are due to *Helicobacter pylori* (87, 143), an intestinal commensal organism that causes ulcers in 5–10% of infected individuals (85). Finally, a common acute condition that emerged in 2019, hypoxemic COVID-19 pneumonia, was rapidly shown to be due to infection with SARS-CoV-2, which causes life-threatening hypoxemic COVID-19 pneumonia in approximately 5–10% of infected individuals (155). These three contrasting examples illustrate the considerable differences in the degree of causality between microbes and the corresponding conditions. The weakly virulent saprophyte *T. whipplei*, the moderately virulent commensal *H. pylori*, and the more virulent airborne SARS-CoV-2 are, however, widely considered to be equally causal.

### 2.2. Clinical and Epidemiological Studies

The first canonical approach follows the nineteenth century tradition and typically involves periodically revisiting the clinical features of the condition studied in patients with the same microbial etiology. Clinical descriptions were enriched as the fields of pathology, laboratory medicine, radiology, and immunology matured. These descriptions gained granularity over time, thereby becoming increasingly useful, in particular with the development of systems immunology (37, 48). They can unravel key steps of diseases, contributing enormously to the understanding of



pathogenesis. For example, the study of multisystem inflammatory syndrome of childhood (MIS-C) has revealed a massive, universal, and specific expansion of V $\beta$ 14 T cells, thereby incriminating T cells in the pathogenesis and raising the possibility that there is a SARS-CoV-2 superantigen (63, 100, 110, 121, 127). Yet these clinical studies fundamentally analyze the consequences of infection, not the causes of disease. They cannot distinguish between the countless consequences of infection to identify the small number of abnormalities present before infection, as almost none of the patients are analyzed before infection. These descriptive studies are also correlative, as they have attempted to identify markers of severity in analyses of the variability of clinical features and outcomes between infected individuals. This approach has given rise to the insightful notion that there may be correlates or proxies of severity, occasionally with high predictive value and biological significance that can help search for root causes of disease. A related approach that is epidemiological in nature involves estimating risk factors for disease at the population level, typically retrospectively and more rarely prospectively (55). Most of these studies have focused principally on the impact of the environment (e.g., the source of microbes and levels of exposure) or of certain demographic factors (e.g., age or sex) on the risk of disease. Moreover, these studies have had a smaller impact on our understanding of infectious diseases than have studies in other fields (e.g., studies of smoking as a risk factor for cancer), as they have only rarely tested the hypothesis of a particular host- or environment-specific factor other than the pathogen being causal for disease. Generally, clinical and epidemiological studies have been immensely helpful medically, particularly for analyses of the impact of preventive or therapeutic measures, but they do not fundamentally call into question the causal role of the microbe and have therefore not attempted to decipher the root causes of severe microbial disease or death from infectious disease.

### 2.3. Experimental Studies In Vivo

A second canonical approach that brings us back to Koch's postulates is the experimental inoculation of animals with microbes. Koch proposed that for a microbe to be validated as a human pathogen, experimental infection with the microbe concerned should result in a condition similar to that seen in humans in at least one animal species. This approach was soon found to be particularly powerful for the study of infectious diseases using an in vivo model, particularly from the 1920s onward, when Leslie Webster (144, 145) carried out experimental infections with various strains of inbred animals. Many different animal models have been developed, but mice are probably the most widely used. We acknowledge the contributions of other animal models, including flies, worms, and fish (57, 112), and are aware of the importance of experimental infections in humans (96, 124). The experimental study of mice has many strengths and some weaknesses as a disease modeling approach, which have been reviewed elsewhere (4, 38, 59, 61, 88, 93, 106, 118, 126, 134, 141). Mice can be used to assess the impact of almost any molecular deficiency (achieved by genetic invalidation or the use of a blocking antibody) on the manifestations and outcomes of infection. What is relevant here is that even excellent models of human disease are rarely designed to decipher the causes of human disease. Reverse genetics studies using knockout mice, like the studies of mice treated with a blocking antibody that preceded them, were often interpreted in the course of alternative approaches but not designed by canonical approaches to test the possibility of rare humans with a similar deficiency being prone to the same or a similar infection. They were typically designed to understand host defense in a typologist manner (molecule A is essential for host defense in humans against microbe B). Yet many of these studies have been successfully interpreted by scientists following an alternative approach providing a rich resource of candidate genes (molecule A is essential for patient P against microbe B). The situation is also different for forward genetics studies, which can be considered an alternative approach, as discussed in

Section 4, as they begin with the observation of interanimal variability during infection and search for its genetic cause (18, 59, 141). Overall, studies of immunity to infection in animal models, especially in knockout mice, have been often interpreted but rarely designed to interrogate interindividual clinical variability during infection.

## 2.4. Experimental Studies In Vitro

The third and most recent canonical approach took off in the 1980s with Falkow and colleagues (94, 131), a decade or two after the birth of cell biology (65). Cells were infected with a microbe in vitro and the consequences of infection for both cell and microbe were analyzed by various microscopic and microbiological means. This reductionist approach benefited from the rise of cell biology, with the description of subcellular compartments at increasingly high resolution due to improvements in microscopy techniques, and the development of molecular microbiology, with the identification and characterization of microbial genes and their products. The impact of microbial infection on both the microbe, in terms of trafficking and replication, and the cell, in terms of subcellular architecture and viability, was studied. Interactions between cells and microbial molecules were also studied. This field of cellular microbiology progressively evolved from studies of the infection of a single cell line and analyses with successive generations of microscopes to the infection of primary cells, induced pluripotent stem cell (iPSC)-derived cells, and, more recently, iPSC-derived 2D and 3D organoids (72, 84). Over the last 50 years, methods of genetic manipulation have been developed for both cells and microbes. This elegant approach, based on a combination of molecular and cell biology and extending across the cell host and microbial worlds, has yielded a treasure trove of information about the interactions between various cells and microbes, including viruses, bacteria, fungi, and even parasites. It has even led to fundamental discoveries in cell biology, as neatly illustrated by the interaction between the human Arp2/3 complex and the *Listeria monocytogenes* ActA protein in actin filament nucleation (146). It has often led to testing hypotheses in vivo in animal models. It has also contributed to the discovery of three examples of Mendelian resistance to infection: CCR5 deficiency preventing infection with HIV, fucosyltransferase 2 (FUT2) deficiency preventing infection with norovirus, and DARC deficiency preventing infection with *P. vivax* (26). However, elegant discoveries in this field have not yet led directly to the elucidation of human genetic determinants of infectious disease. This approach was not conceived for the study of interindividual clinical variability, probably because clinical variability is a key problem at the organism and population levels but not at the cellular level. One can, however, surmise that these elegant and rigorous studies will provide a wealth of information for alternative approaches.

## 3. THE ALTERNATIVE APPROACHES: MICROBIAL INFECTION REVEALS A PREEXISTING CAUSE OF DISEASE

Alternative approaches search for preexisting causes of disease in populations of highly diverse individuals infected with a trigger microbe.

### 3.1. Acquired Immunodeficiencies

Alternative approaches consider the cause of disease and death to lie in the host and to be present before infection. The best-known paradigm in this respect is, paradoxically, also the most recent and least expected: acquired immunodeficiencies. From the 1960s onward, immunosuppression resulting from chemotherapy for cancers and therapeutic immunosuppression in the context of organ transplantation revealed that myeloid and lymphoid alterations underlie not only specific but also opportunistic infections (i.e., infections observed preferentially or exclusively in patients

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**Odds ratio (OR):**

ratio of the odds of disease in the exposed group to the odds of disease in the nonexposed group

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with overt immunological abnormalities) (27). A couple of decades later, HIV infection emerged, providing tragic and compelling evidence that infectious diseases may be caused by immunodeficiencies. In both cases, distinctive immunological abnormalities (e.g., neutropenia, CD4<sup>+</sup> lymphopenia) connected causes (e.g., immunosuppression, HIV infection) with infectious consequences (e.g., fungal or mycobacterial diseases). Neither set of observations had been predicted (24), and perhaps as a result, neither was interpreted, even speculatively, as heralding a paradigm shift. For opportunistic infections, however, the occasional absence of known immunodeficiency in some patients led to these cases being designated idiopathic, perhaps as an attempt to stress that they were unexplained but that an explanation should be sought. Nevertheless, these observations did not call into question the notion that specific infections were caused primarily by specific pathogens. Even though the risk of tuberculosis is 20–30 times higher in patients with HIV and a lack of circulating CD4<sup>+</sup> T cells (54), and despite up to 6.3% of cases of tuberculosis worldwide being attributable to HIV infection (148), the remaining 93.7% of cases are still seen as being caused by *Mycobacterium tuberculosis*. Overall, despite the millions of deaths from infection due to the two types of acquired immunodeficiency, the global perception of the scientific community underwent merely superficial alterations, with no fundamental change. Opportunistic infections were seen as a consequence of immunodeficiency, but classic specific infections were not. Both opportunistic infections and overt, acquired immunodeficiencies were seen as exceptions, despite the large number of patients affected. The idea that death from infection attests to an immunodeficiency, whether overt or covert, did not emerge from these powerful studies, demonstrating the extent to which the classical paradigm is engrained.

### 3.2. Population- and Ancestry-Based Genetic Studies

Another alternative approach, which has remained well below the microbiological radar, predates the discovery of acquired immunodeficiencies. From 1909 onward, Karl Pearson (108) and the school of biometricians, later rebranded as population geneticists, suggested that human infectious diseases had a strong hereditary component. Particularly compelling evidence was provided by a series of twin studies of tuberculosis conducted in the 1930s and 1940s (117) that showed that concordance rates for tuberculosis were much higher in identical (monozygotic) than in fraternal (dizygotic) twins (68). The transition from classical to molecular studies in this statistical branch of genetics started and culminated with Anthony Allison's (5) landmark discovery that the sickle cell trait confers 10-fold protection against life-threatening malaria due to *Plasmodium falciparum* (135). This observation made sense mechanistically, as erythrocytes carry the parasite. However, over subsequent decades, this population- and ancestry-based approach failed to reveal stronger associations through candidate or genome-wide association studies (29). One of the most remarkable results was the finding that the chances of clearing HCV infection are three and six times higher in individuals heterozygous and homozygous, respectively, for a variant at a type III interferon locus (52, 136). The mechanism of resistance is not entirely clear, although type III interferons are expressed in the liver (137). Most other studies have reported more modest odds ratios (ORs), generally below 2, except for certain HLA class I alleles associated with AIDS progression with hazard ratios for protection of approximately 0.3 (69). It remains unclear why population-based approaches have not lived up to expectations and yielded stronger molecular and cellular connections between germ line genotypes and infectious phenotypes. Perhaps the best explanation is the high level of genotypic and phenotypic heterogeneity in large populations of patients (26, 29). Another explanation is that these studies have typically focused on common variants, as opposed to rare variants, and have therefore been better at identifying modifier genes rather than causal variants. With hindsight, these studies have proved more suitable for

assessing the impact of microbes on human genomes at the population level (e.g., the selection of DARC-deficient individuals by *P. vivax* or that of hemoglobin AS heterozygotes by *P. falciparum*), as initially speculated by Haldane (60), than for detecting genetic variants underlying infectious diseases at the individual level. As in other fields of human genetics, population genetics of infectious diseases has turned out to be of greater relevance to evolutionary studies than to physiological studies (120).

### 3.3. Patient- and Family-Based Genetic Studies

Patient- and family-based approaches have been more productive from a physiological and pathological angle. These studies were initiated by the Mendelians, including Archibald Garrod (51), who suggested that severe infectious diseases can be genetically driven. However, the field moved directly into the molecular genetic era in the 1950s, with the description of Mendelian cosegregation for immunological and infectious phenotypes. Rolf Kostmann (76, 77) reported autosomal recessive neutropenia as the first IEI (32), and Ogden C. Bruton (22) and David Gitlin (56) described X-linked recessive agammaglobulinemia shortly thereafter (66). The discovery of causal genes began in 1985 (29). The IEIs concerned were rare, Mendelian, and responsible for both immunological and infectious phenotypes, invariably including multiple infections. A second step forward was made in 1996 with the discovery of the first molecular basis for a Mendelian infection (i.e., monogenic with complete penetrance): Mendelian susceptibility to mycobacterial diseases (MSMD) (67, 102). A third step forward was taken in 2007 with the description of the molecular basis of the first monogenic non-Mendelian (i.e., monogenic with incomplete penetrance) infection: herpes simplex encephalitis (HSE) (153). The genetic study of rare infections led to that of common infections (29). The genetic dissection of MSMD led to the identification of rare IEIs underlying rare cases of tuberculosis, which in turn led to the discovery of a common IEI (homozygosity for P1104A *TYK2*) in approximately 1% of cases of tuberculosis in patients of European descent (20, 70, 71). With the identification of causes and mechanisms, there was a gradual shift from studies of rare disorders of immunity to studies of common genetic determinants of infection (29). Each infectious disease, whether rare or common, can apparently be driven by the disruption of one essential mechanism, which may be specific to that infection [private; e.g., X-linked recessive TLR7 deficiency, which underlies critical COVID-19 but not influenza or HSE] (8, 28) or, more often, nonspecific [public; e.g., mutations of the type I interferon receptor underlying HSE and influenza or COVID-19 pneumonia] (28). The severity of the biochemical phenotype also has a direct impact on the virulence level of the microbial threat. The disruption of type II interferon immunity underlies MSMD due to weakly virulent mycobacteria, whereas milder defects of type II interferon underlie tuberculosis due to more virulent mycobacteria (33). Remarkably, these findings have implicated particular pathogenic pathways in the diseases observed in other patients with the same infections, including patients with acquired immunodeficiencies or other inherited immunodeficiencies (151).

### 3.4. Autoimmune Phenocopies

The study of IEIs took a surprising turn when cytokine-neutralizing autoantibodies were shown to phenocopy inborn errors of the corresponding cytokines (34, 114). The first example (2004) was provided by autoantibodies neutralizing type II interferon, which underlies clinical disease caused by weakly virulent mycobacteria, mimicking MSMD (42, 62). The second example (2008) was the neutralization of IL-6, which like IL-6R deficiency underlies staphylococcal disease (116). The third example (2010) was the development of chronic mucocutaneous candidiasis in patients with autoantibodies against IL-17A/F (73, 115). Autoantibodies neutralizing granulocyte-macrophage

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**Penetrance:** proportion of individuals carrying a particular genotype that expresses a particular phenotype (e.g., an infectious disease)

**MSMD:** Mendelian susceptibility to mycobacterial diseases

**HSE:** herpes simplex encephalitis

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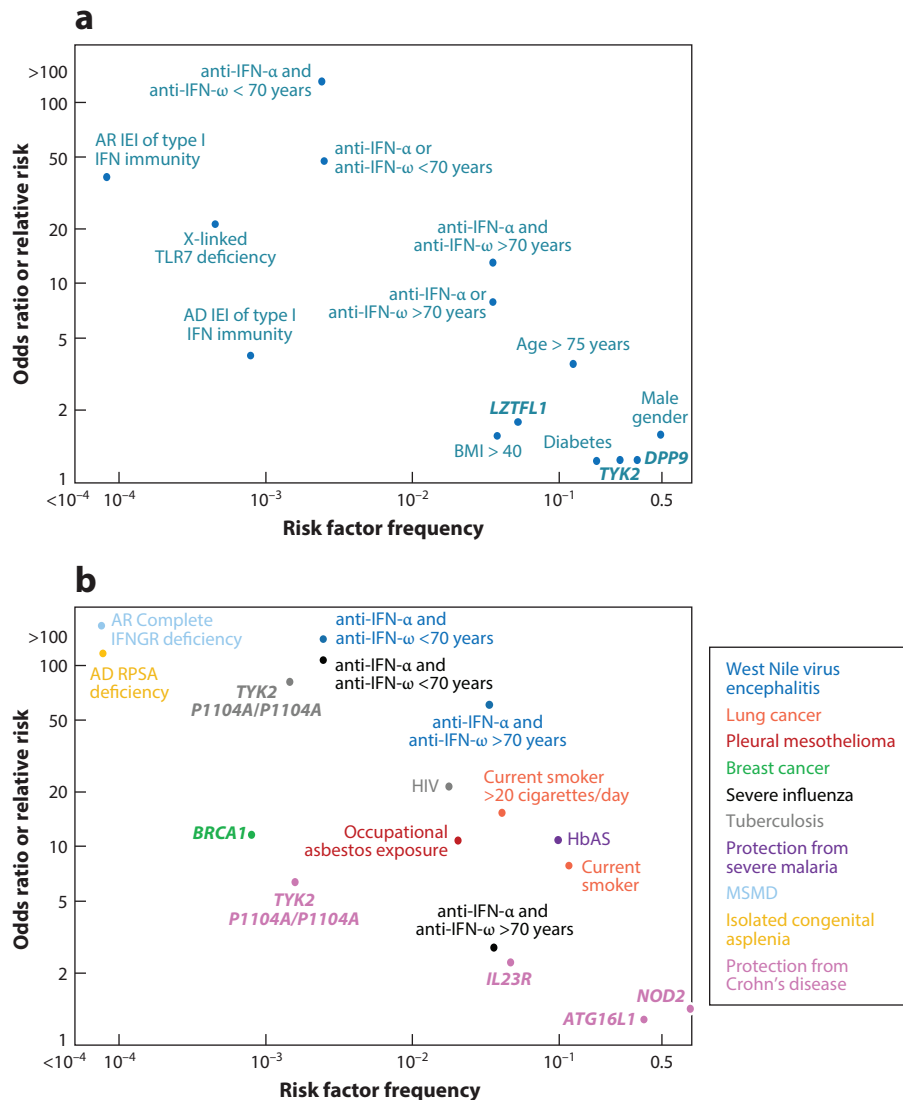
colony-stimulating factor (GM-CSF) were shown in 1999 to underlie pulmonary alveolar proteinosis (PAP) (74) and also subsequently in 2012 to underlie *Nocardia* or *Cryptococcus* disease. Both infections, like PAP, result from an impairment of alveolar macrophage function, which is dependent on GM-CSF (119). Finally, autoantibodies against type I interferons, which were first reported in the early 1980s but thought to be silent (140), have been shown since 2020 to underlie various life-threatening viral diseases, including, in particular, 15% of cases of critical COVID-19 pneumonia (13, 15, 114), one-third of the rare but severe adverse reactions to the yellow fever live-attenuated virus (14), 5% of cases of critical influenza pneumonia (152), 24% of cases of critical Middle East respiratory syndrome pneumonia (6), and 40% of cases of West Nile virus (WNV) encephalitis (53). These viral infections can be caused by the same autoantibodies against type I interferons, which neutralize the 12 IFN- $\alpha$  and/or IFN- $\omega$  subtypes and, more rarely, IFN- $\beta$ . The autoantibodies are present in the general population at a prevalence that remains stable until age 65 (0.3–1%), subsequently rising sharply to reach 4–8% in the elderly (13). These autoantibodies neutralize the cytokine, precede infection, and cause disease (86). Uncovering the genetic cause and mechanism of critical influenza pneumonia in a single child with inherited IRF7 deficiency in 2015 (35) led step by step to the identification of the cause of WNV encephalitis in 40% of cases in 2023 (53). These findings actually resulted from the convergence of two older lines of research on human inborn errors of type I interferon, beginning in 2003, and autoantibodies against type I interferons in patients with autoimmune polyendocrinopathy syndrome type 1 and biallelic germ line null mutations in *AIRE*, beginning in 2006 (30). These autoantibodies can be considered strong (150 > OR > 10), common (>100 million individuals worldwide), public (viral pneumonia, viral encephalitis), and universal (across ancestries) determinants of severe viral diseases (29).

#### 4. CONCLUDING REMARKS

The studies performed over the last 30 years have revealed human genetic and immunological determinants of a growing number of severe infectious diseases in a growing proportion of patients. Each infection studied seems to involve a core mechanism with physiological homogeneity even in situations of genetic heterogeneity. However, this does not imply that different infections do not share causes and mechanisms of disease. For example, inborn errors of type II interferon immunity can underlie diseases due not only to different mycobacteria (*Mycobacterium avium*, *Mycobacterium chelonae*, etc.) but also to different intramacrophagic infectious diseases (*Mycobacterium*, *Salmonella*, etc.), whereas some inborn errors of type I interferon immunity can underlie different viral diseases in different tissues (pneumonia due to influenza or coronavirus, or HSE, etc.). Mutations of *TLR3* can underlie HSE or influenza pneumonia (82, 153). Infectious diseases can therefore be allelic, consistent with early forward genetics studies of mice that showed *Bcg*, *Ity*, and *Lsb* to be allelic at the *Nramp1* locus (130, 142). More generally, they can be caused by deficits of the same mechanism of defense, whether of genetic or nongenetic origin. Neutralization of type I interferons by autoantibodies can impair host defense against various viruses in various organs (16, 154). Both COVID-19 pneumonia and WNV encephalitis can be caused by autoantibodies against type I interferons (15, 53). There are, however, more specific, perhaps even private, pathways, as illustrated by the hitherto unknown specificity of COVID-19 pneumonia due to X-linked recessive TLR7 deficiency (8) or *EVER1-EVER2-CIB1* mutations in patients vulnerable to beta human papillomavirus infections (39). Overall, there seems to be one key defective molecular pathway or cellular circuit per disease across patients. Some sections of this pathway may be common to other infections, whereas other sections are specific. The intensity of the deficit also has an impact, especially when the corresponding pathogens vary in virulence. Type II interferon immunity is a quantitative trait relative to the virulence of mycobacterial species, with complete

defects underlying clinical disease due to weakly virulent mycobacteria and partial defects underlying tuberculosis, which is caused by a mycobacterium that is 1,000 times more virulent (tuberculosis strikes less than 1 in 10 individuals infected with *M. tuberculosis*, while BCG vaccines and environmental mycobacteria cause disease in less than 1 in 10,000 individuals), but not disease due to less virulent species (19, 33, 44). Finally, the proportion of cases for which a causal explanation can be found is unprecedented, reaching 40% for WNV encephalitis, with ORs to develop disease for carriers of autoantibodies against type I interferons on the order of 100 (53).

This last finding raises important questions of general relevance. How can we define causality, especially in the absence of complete penetrance in infected individuals, for rare and common variants (17, 91, 107, 149)? Which OR threshold should be used to define causality (Figure 3a,b)? When there is no OR, where do we define the threshold for causality based on the study of only



(Caption appears on following page)

**Figure 3** (Figure appears on preceding page)

A selection of genetic or nongenetic risk factors associated with critical COVID-19 pneumonia or other conditions. (a) Odds ratios (ORs) for critical COVID-19 associated with epidemiological risk factors were obtained from Reference 150, with X-linked TLR7 deficiency from Reference 8, with the three most significant common variants (*LZTFL1*, *DPP9*, *TYK2*) from Reference 36, with autosomal recessive (AR) or autosomal dominant (AD) inborn errors of immunity (IEIs) from Reference 90, and with autoantibodies neutralizing 10 ng/mL IFN- $\alpha$  and/or IFN- $\omega$  from Reference 13. (b) Effects of genetic and nongenetic risk factors on other conditions. Relative risks (RRs) for lung cancer were obtained from Reference 105, for breast cancer from Reference 139, and for tuberculosis with HIV infection from References 54 and 79. ORs for severe influenza were obtained from Reference 152; for West Nile virus encephalitis from Reference 53; for isolated congenital asplenia from Reference 21; for pleural mesothelioma from Reference 80; for protection against severe *Plasmodium falciparum* malaria, with a frequency of hemoglobin AS (HbAS) from the African samples of the 1,000 genomes database, from Reference 135; for tuberculosis in P1104A *TYK2* homozygotes, with a frequency of homozygotes observed in the European population, from Reference 20; for protection from Crohn's disease, with the three most significant common variants, from Reference 50; and for P1104A *TYK2* homozygotes from Reference 41. An OR of  $>100$  is also indicated for AR complete IFN- $\gamma$  receptor (IFNGR) deficiency, for which there are more than 150 patients with complete penetrance for the syndrome of Mendelian susceptibility to mycobacterial diseases (MSMD).

a few or even a single patient? What is the relationship between OR and relative risk (RR) and between RR and clinical penetrance? The RR, for which interpretation is the simplest, is the ratio of the risk of disease in the exposed group (e.g., carriers of the at-risk genotype or of autoantibodies) to the risk of disease in the nonexposed group (e.g., noncarriers), whereas the OR is the ratio of the odds of disease in the exposed group to the odds of disease in the nonexposed group. The OR, which is widely calculated in case-control studies, approaches the RR when the prevalence of the disease is low (classically less than 10%) (58). Mathematically, an RR greater than 10 for a risk factor present before the onset of disease can probably be seen as a threshold for causality, as it is difficult to imagine any bias or confounding factor that might account for such a high RR (101); the higher the RR is, the stronger and more likely the causality will be. RR and penetrance are closely related; this relationship depends on the frequency of the at-risk genotype and the prevalence of the disease (3). In particular, for a rare disease such as HSE or MSMD ( $<10^{-4}$ ), a strong RR (e.g., 500) can be associated with only modest penetrance (e.g., 0.05). This mathematical approach to causality is best suited to studies of multiple patients and is facilitated by genetic homogeneity (3). Mechanistically, causality can be considered to occur when a thread of experimentally documented causes and consequences connects a genotype with a phenotype; this may also occur in studies of single patients, which have played an instrumental role in the discovery of IEIs (31). The search for causality and mechanisms in individuals, which is at the heart of the search for IEIs, also contrasts with the search for correlations without mechanisms, which has historically guided population genetics studies (17, 24, 91, 107, 149).

Bearing this new knowledge in mind, one can look backward with the benefit of hindsight. The unusually high medicine-to-science ratio for impact in the field of infectious disease is unique but perhaps gradually normalizing, thanks largely to the patient- and family-based studies conducted over the last 30 years. Infections can be prevented by vaccination and hygiene and cured by surgery and medicines, but we have known too little for too long about their pathogenesis. In this light, the finding that the neutralization of the 12 IFN- $\alpha$  subtypes and/or IFN- $\omega$  by autoantibodies can underlie as many as 40% of WNV encephalitis cases is remarkable (53). Causality is clear in this case, with an OR on the order of 100 and a preexisting molecular mechanism involving a deficiency of type I interferon immunity. This observation has many far-reaching clinical implications for the screening or diagnosis of populations or individuals at risk, in general, and the development of new preventive or therapeutic approaches, in particular. The development of host-directed therapies will serve as a source of hope for other major diseases, such as tuberculosis and malaria,

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**Relative risk (RR):**

ratio of the risk of disease in the exposed group (e.g., carriers of the at-risk genotype or of autoantibodies) to the risk of disease in the nonexposed group (e.g., noncarriers)

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for which there are currently no efficient vaccines and for which resistance to antimicrobial drugs is increasing (33). The science of infectious diseases is perhaps now finally in a position to envisage closing the gap with the medicine of infectious diseases. The current situation contrasts with most other medical fields, in which science is ahead of medicine, but an analogy relating to allergy comes to mind. Allergic conditions can be prevented by removal of the allergen or desensitization. They can be treated with antihistamines and anti-inflammatory drugs, or with epinephrine in the most severe cases. But our understanding of most allergies, from peanut allergy to celiac disease, remains poor. A line of research similar to that in the field of infectious diseases has recently taken off, with the identification, for example, of de novo *STAT6* gain-of-function mutations with complete penetrance in multiple kindreds of various ancestries (10, 129, 132, 133). The family-based search for IEs underlying infectious or allergic disease is promising and may eventually relegate microbes and allergens to the status of environmental triggers.

We can now also look forward with cautious optimism and consider the infectious diseases due to approximately 3,000 microbial species, in billions of patients, for which the causes and mechanisms remain to be deciphered. The findings reported over the last 30 years provide a roadmap for future research. There is every reason to believe that rare and common IEs can be discovered in patients with rare or common infections. The obstacles to this research are perhaps more psychological than scientific, and they include, in particular, the sociology of the scientific community (78, 109, 138). Typology has dominated biological research since the development of molecular biology, probably under the influence of physicists. The famous quote “all science is either physics or stamp collecting,” widely attributed to Ernest Rutherford, to which Jacques Monod added, “What is true for *Escherichia coli* is true for the elephant,” has been taken as a fundamental and correct critique of the historically nominalist nature of biology. The idea that there is a uniform host is consistent with this tradition and of course antinomic to the reality that there are more than 7 billion different human beings. The nominalist approach is still neglected in biology, despite its historical roots dating back to Charles Darwin’s critique of a fixed species concept and Claude Bernard’s critique of statistics in biology, and the more recent “chemical individuality” of Garrod (51) and “population thinking” of Mayr (26, 92). The case report and single-patient studies are not deemed of interest for biologists in search of general principles, as they are seen as stamp collecting. However, interindividual variability is in itself a nominalist problem—and not a minor problem, as it is perhaps the quintessential biological and clinical problem—and a very challenging one. Admittedly, studying billions of patients one by one would be a daunting task, but the study of individual patients, and of individual families, has a high return on investment. Indeed, the patient-based search for causality and mechanism, sometimes in single patients, can yield results of broader significance. A striking example is the discovery that countless patients die from viral disease because of preexisting autoantibodies against type I interferons (13, 53, 86, 152). This discovery was directly derived from lines of research into rare diseases, including the 1981–1984 case report published by Gresser and colleagues (98, 111). In-depth studies of single patients have proved so far the best approach to uncovering the infection enigma at the population level.

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