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Lethal Infectious Diseases as Inborn Errors of Immunity: Toward a Synthesis of the Germ and Genetic Theories

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Abstract

It was first demonstrated in the late nineteenth century that human deaths from fever were typically due to infections. As the germ theory gained ground, it replaced the old, unproven theory that deaths from fever reflected a weak personal or even familial constitution. A new enigma emerged at the turn of the twentieth century, when it became apparent that only a small proportion of infected individuals die from primary infections with almost any given microbe. Classical genetics studies gradually revealed that severe infectious diseases could be driven by human genetic predisposition. This idea gained ground with the support of molecular genetics, in three successive, overlapping steps. First, many rare inborn errors of immunity were shown, from 1985 onward, to underlie multiple, recurrent infections with Mendelian inheritance. Second, a handful of rare and familial infections, also segregating as Mendelian traits but striking humans resistant to other infections, were deciphered molecularly beginning in 1996. Third, from 2007 onward, a growing number of rare or common sporadic

infections were shown to result from monogenic, but not Mendelian, inborn errors. A synthesis of the hitherto mutually exclusive germ and genetic theories is now in view.

INTRODUCTION

The Continuous Threat of Human Infectious Diseases

Fevers killed approximately half of all humans before the age of 15 years worldwide for about 200,000 years of human evolution, until the late nineteenth century (1). Following the establishment of the germ theory of disease between 1865 and 1885 (2, 3), it became widely accepted that life-threatening fevers in humans were typically infectious. The conquests that followed the germ theory have gradually prolonged our life expectancy at birth, from approximately 20 to approximately 80 years (1). Indeed, hygiene, aseptic surgery, vaccines, serotherapy, and pharmacological treatments have successfully prevented or cured diverse viral, bacterial, fungal, and parasitic infections. However, it may not be sufficient to rely exclusively on these approaches to combat human infections, because (*a*) they have been unsuccessful for a number of deadly common infectious diseases, (*b*) anti-infectious agents (and, to a lesser extent, vaccines) inevitably select resistant microbes by natural selection (at a rate potentially exceeding that at which we can develop new drug treatments and vaccines), and (*c*) new infectious diseases inevitably emerge (the transmission of which is facilitated by modern lifestyles) through inadvertent exposure to existing pathogens, particularly those present in animals, or the generation of new pathogens through genetic shifts. There are already a number of alarming signs, such as (*a*) the persistent failure to develop vaccines against human immunodeficiency virus, tuberculosis (TB), and malaria (4); (*b*) the spread of drug-resistant *Mycobacterium tuberculosis* and pneumococcal serotypes not covered by current vaccines (5); and (*c*) recent pandemics of coronaviruses, Ebola virus, and influenza viruses (6). The current intervention paradigm may therefore need to be upgraded. Microbe-centered approaches may not sustainably ensure that human life expectancy remains at current levels. It would be prudent to consider the arms race between humans and microorganisms as a long-term affair, and not to take our apparent success for granted.

Interindividual Variability in the Course of Infection

The development of alternative approaches for preventing and treating infectious diseases is thus timely. One promising avenue of research is rooted in the pathogenesis of infectious diseases themselves. Indeed, the key but neglected problem in the field of infectious diseases was posed at the turn of the twentieth century, with the discovery of latent (nonreplicating) and unapparent (replicating) infections in asymptomatic individuals (7). This discovery led to the recognition that most infectious agents kill only a small proportion (8), typically a very small proportion, of infected individuals. In this context, what is the root cause of life-threatening infectious diseases? This so-called infection enigma is paradoxical (9), as the view that infectious diseases are understood is widespread in both lay and learned circles. The very names of these conditions proclaim their infectious nature, and, as such, they are regarded as prototypical environmental conditions. However, the clinical variability between individuals infected with any given human pathogen is enormous, ranging from silent to fatal infections (8). Indeed, until the late nineteenth century the colossal burden of infectious diseases resulted largely from the diversity of infectious agents rather than from their individual virulence (10, 11). One child would die of smallpox, another of diphtheria, a third of malaria, and so on. Epidemics or pandemics would have modified these proportions only

transiently. In a given historical period and geographic area, only a few emerging or reemerging pathogens killed a sizable proportion of infected individuals, such as the European plague in the Middle Ages (12). The proportion of the population wiped out only rarely exceeded 30% (13, 14). If death is a rare outcome of infection with most microbes, how can we explain the pathogenesis of lethal infectious diseases? Infectious agents trigger infectious diseases and are necessary but not sufficient for their development. As René Dubos (15) put it in 1955, we should have "second thoughts on the germ theory."

History of the Genetic Theory of Infectious Diseases

Well-known factors conferring a predisposition to severe infectious diseases include acquired immunodeficiencies, whether caused by immunosuppressive drugs (e.g., in the context of autoimmunity or transplantation) (16), by microbes themselves (e.g., following infection with human immunodeficiency or measles virus) (17, 18), or by severe conditions (e.g., cancers or malnutrition) (19, 20). In certain regions of the world, these risk factors account for a sizable proportion of lethal infections. This observation itself actually suggests that severe infections in other patients without overt acquired immunodeficiency may be favored by other, covert immunodeficiencies. Indeed, any lethal infection, by definition, attests to an immunodeficiency of the particular patient during the specific encounter with the causal infectious agent. In principle, this immunodeficiency in an otherwise healthy human who is apparently but not actually immunocompetent may be a consequence of qualitative or quantitative variation in the pathogen (the microbial theory), variations of the conditions of infection (the ecological theory), or variations of the adaptive immune response to related infectious antigens in the past and present (the immunological theory) (11). Somatic variations in cells other than T and B lymphocytes may also contribute to interindividual variability in host defense (a broad somatic theory). All these explanations have been validated, at least in specific instances, but none of them can fully explain interindividual variability in a given ecosystem, settlement, building, or household. Moreover, they are difficult to test at a large scale. We have previously reviewed (11) the history of a fourth theory (i.e., the genetic theory), according to which severe infectious diseases can be due to inborn errors of immunity (IEIs) (21). We have discussed elsewhere (8, 11) the long gestation of this theory, from the turn of the nineteenth century onward, and the key advances made with classical genetics in the first half of the twentieth century.

The Genetic Theory from 1946 Onward

In this review, we focus on the modern era (1946–2020), which is defined by cells and molecules, analyzing the successive overlapping steps leading to the model discussed here, according to which life-threatening infectious diseases of both children and adults can result from single-gene (monogenic) IEIs that rarely display complete penetrance (i.e., that are rarely Mendelian) (9–11, 21, 22). We do not review Mendelian conditions, such as sickle cell disease and cystic fibrosis, which immunologists do not generally regard as IEIs, although they are evidently inborn errors underlying lethal infections (23). This review also does not deal with population-based association studies yielding modest relative risks, as none of these studies have ever matched the 1954 discovery of the sickle cell trait increasing resistance to severe malaria by a factor of 10 (24). Finally, this review does not cover the small number of fascinating examples of Mendelian resistance to infectious agents, with inherited deficiencies of DARC, CCR5, and FUT2 underlying resistance to *Plasmodium vivax*, human immunodeficiency virus, and norovirus, respectively (11, 25). Rightly or wrongly, these three lines of research have not been incorporated into the field of IEIs. Instead, we attempt to understand how gradual paradigm shifts have led to the current model. We discuss how

the seminal reports of the first IEI between 1946 and 1952 gradually led to the current notion that severe infectious diseases in humans can be due to single-gene IEIs with incomplete penetrance. We suggest that this field has progressed toward a synthesis of the infectious (thesis) and genetic (antithesis) nature of severe fevers in three large steps, corresponding to three types of IEIs, which we refer to as primary immunodeficiencies (PIDs) (the underlying genetic defects of which were discovered from 1985 onward), Mendelian infections (from 1996 onward), and monogenic but not Mendelian infections (from 2007 onward).

STEP ONE: PRIMARY IMMUNODEFICIENCIES

The Birth of Primary Immunodeficiencies

The blueprint for conventional IEIs, commonly referred to as PIDs, is widely agreed to be the description of Bruton's X-linked recessive (XR) agammaglobulinemia in 1952 (**Table 1**) (**Figure 1**)

Table 1 Three categories of IEIs underlying severe infectious diseases

Characteristics	Primary immunodeficiencies[a]	Mendelian infections[b]	Monogenic infections[c]
Number of patients	Known (intermediate)	Known (small)	Unknown (large?)
Familial cases	Common	Common	Rare (sporadic)
Penetrance	High or complete	High or complete	Low
Age at onset	Children ≫ adults	Children > adults	Children or adults
Number of infectious agents	High	Single (or a few)	Single
Number of infectious episodes	High (acute or chronic)	Low or high	Low
Infectious diseases	Often rare, opportunistic	Rare, idiopathic	Common
Immunological abnormalities	Before gene discovery	After gene discovery	After gene discovery
Cell types involved	Leukocytes	Leukocytes or other cell types (e.g., keratinocytes and *CIB1*)	Leukocytes or other cell types (e.g., cortical neurons and *TLR3*)
Other clinical phenotypes	Common (autoimmunity, allergy, autoinflammation, cancer, others)	Rare (syndromic forms)	Very rare
Examples	AR SCID and variations in *RAG1* XR agammaglobulinemia and *BTK* AD congenital neutropenia	AR EV and variations in *CIB1* XR EBV disease and *SAP* AD MSMD and *IFNGR1*	AR severe influenza pneumonitis and variations in *IRF7* XR invasive pneumococcal disease and *NEMO* AD HSE and *TLR3*

[a]Primary immunodeficiencies comprise more than 400 monogenic IEIs disrupting host defense against various infectious agents. They are also associated with overt immunological abnormalities. They typically display high or complete immunological and clinical penetrance.
[b]Mendelian infections are five monogenic IEIs that disrupt host defense against one or a few infectious agents. The infections were idiopathic until the discovery of disease-causing genes led to the recognition of immunological abnormalities. Their clinical penetrance is high or complete.
[c]Monogenic infections comprise at least 10 monogenic IEIs that disrupt host defense against one or a few infectious agents. These infections also typically remained idiopathic until the discovery of disease-causing genes. Their penetrance is low (hence their mode of inheritance in parentheses), accounting for these infections being typically sporadic, as opposed to familial. Importantly, variations at a given locus can underlie the three types of phenotypes, as neatly illustrated by variations at the *NEMO* locus (148, 150).
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EBV, Epstein–Barr virus; EV, epidermodysplasia verruciformis; HSE, herpes simplex encephalitis; IEI, inborn error of immunity; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency; XR, X-linked recessive.

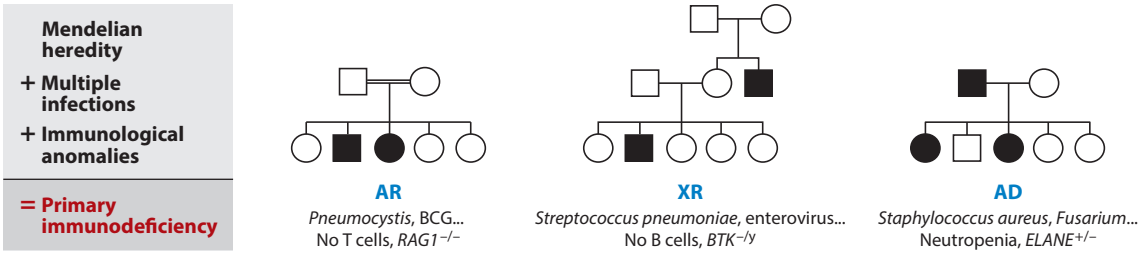

Figure 1

Pedigrees for primary immunodeficiencies for the three modes of inheritance: autosomal recessive (AR), with the example of severe combined immunodeficiency due to RAG1 deficiency (the double line indicates that the parents are consanguineous); X-linked recessive (XR), with the example of agammaglobulinemia due to BTK deficiency; and autosomal dominant (AD), with the example of severe congenital neutropenia due to ELANE deficiency. Primary immunodeficiencies are typically characterized by multiple infections, overt immunological abnormalities, and a high penetrance (see **Table 1**). Squares indicate males, circles indicate females, filled shapes indicate affected individuals, and unfilled shapes indicate unaffected individuals.

(26–28). Patients with this condition had an immunological phenotype of serum agammaglobulinemia, which had only recently become detectable with the advent of electrophoresis. Their infectious phenotype consisted of invasive pneumococcal and other pyogenic bacterial infections, which were recurrent and/or multiple, an observation made possible by the advent of antibiotics. These two phenotypes cosegregated as an XR trait. Severe congenital neutropenia had been described earlier, in 1950, in children with severe staphylococcal and other bacterial infections and congenital neutropenia, two phenotypes that cosegregated as an autosomal recessive (AR) trait (29, 30). Hereditary agranulocytosis was not listed in the international classification of PIDs until 1999, because neutrophils were studied by hematologists, not immunologists (31). It is telling that the field did not adopt the term AR staphylococcal disease or XR pneumococcal disease to describe these conditions; instead, the emphasis was placed on immunological abnormalities, because they were thought to be causal and rarer than the corresponding infections. With hindsight, the first human IEI to be described was actually epidermodysplasia verruciformis (EV), which was defined in 1946 as an AR form of disseminated warts caused by unidentified viruses (32). The lack of a detectable immunological or hematological phenotype prevented this dermatological condition from being seen as an IEI until 2004 (31). The identification of an immunological abnormality has historically been the key to the detection, designation, and classification of PIDs, to a much greater extent than the associated clinical phenotype, infectious or otherwise. For example, immunoglobulin A (IgA) deficiency, which is common and often asymptomatic, was considered to be a PID, despite its low clinical penetrance, as soon as it was discovered in the late 1960s (33, 34). Moreover, hyper-IgE syndrome (HIES) was named after patients' high serum IgE levels, which do not underlie the patients' life-threatening infectious phenotype and may not even underlie their severe eczema (35).

Immunological Phenotypes of Primary Immunodeficiencies

Other immunological phenotypes, such as the lack of a spleen (1956) (36), lymphocytes (1958) (37), or thymus (1965) (38), paved the way for the description of many more defects of the development of specific lymphocyte subsets, such as T and B lymphocytes, or $CD4^+$ or $CD8^+$ T lymphocytes (39, 40). This, in turn, led to the description of functional deficiencies of lymphocytes in other patients with normal lymphoid development. Following the discovery of neutropenia, chronic granulomatous disease and other quantitative or qualitative inborn errors of myeloid

cells were progressively discovered. The many Mendelian disorders of complement were also soon considered as PIDs, from 1965 onward, even though most complement proteins are synthesized in the liver by hepatocytes (23). The International Union of Immunological Societies (IUIS) classification of PIDs is still structured on the basis of these immunological phenotypes, which have accompanied the development of the field of IEIs for 70 years. The successive classifications have also been structured around the innate/adaptive dichotomy. This immunological concept, which holds at the cellular level, with adaptive immunity restricted to T and B cells, does not translate easily to the genetic level, as very few immune system genes can be said to be purely adaptive (i.e., expressed and functional only in T or B cells), and only slightly more can be considered purely innate (i.e., expressed only in other types of circulating or tissue leukocytes). Most PIDs affect both innate and adaptive leukocytes. It is even harder to adhere to this dichotomy genetically if innate immunity is considered in its broad sense, encompassing both leukocytes and other cell types. Indeed, a growing number of genetic etiologies have been shown to affect both leukocytes and other cell types. Moreover, genetic defects of nonhematopoietic cells may profoundly impair the development of certain leukocytes, as neatly illustrated by inborn errors of the thymic stroma, which prevent the development of T cells (38, 41).

Infectious Phenotypes of Primary Immunodeficiencies

The clinical phenotypes of PIDs are typically infectious; the term immunodeficiency indicates an insufficient capacity to fend off microorganisms. These PIDs are unusual in their breadth, with multiple and recurrent infections, including viral, bacterial, fungal, and parasitic infections, and also in their depth, with often severe and sometimes rare infections (42). Bruton's index case had suffered from 19 episodes of invasive pneumococcal disease, each of which had been cured by antibiotics (26). Until antibiotics became available, the first life-threatening bacterial infection in such patients was almost invariably lethal; recovery from these infections revealed a completely new and unsuspected phenotype in a small proportion of cases. Most of the infectious diseases observed in patients with PIDs are not natural phenotypes; they occur both because of and despite medical intervention. The infections of PID patients are both recurrent and multiple, whereas most individuals without suspected PID typically suffer from one or at most two or three life-threatening infections in their lifetime, very rarely caused by the same microbe. The infections of PID patients are also often rare and unusual, and sometimes opportunistic, that is, considered to occur preferentially or almost exclusively in patients with a detectable immunological abnormality (whether inherited or acquired) (42). Severe infections that are rare (or opportunistic), recurrent, or multiple are almost universally deemed sufficient to prompt the search for immunological deficits in the patient, and a family history of these deficits leads to a search for Mendelian inheritance (**Figure 1**). Once infectious and immunological phenotypes have been connected in sporadic cases, and even more so by Mendelian inheritance in multiplex kindreds, a PID is suspected and subsequently diagnosed or discovered. This field has been extraordinarily successful, with probably more than 300 of the 430 known IEIs meeting this definition (39, 40, 43).

Other Clinical Phenotypes of Primary Immunodeficiencies

Before moving on to a discussion of the mechanisms of infection in patients with PIDs, we note that the field of IEIs in general has also grown horizontally, with the discovery of four other major categories of clinical phenotypes: autoimmunity, autoinflammation, allergy, and cancer. The first autoinflammatory phenotype to be described was probably angioneurotic edema in 1965 (44, 45); the first allergy was probably HIES in 1974 (35, 46); the first autoimmunity phenotype

was probably complement deficiency in 1972 (47, 48); and the first cancer was probably ataxia telangiectasia in 1964 (49). The description of cancers in patients with PIDs did not call into question the status of these conditions as PIDs. Many such cancers are virus driven, at least those favored by the immunological disorder itself, whereas most of the others are due to DNA repair disorders that compromise both immunity and cell growth. Allergy, autoimmunity, and autoinflammation, occasionally referred to collectively as immunological dysregulation, recently led the community to embrace the broader term IEI, in preference to PID (39, 40, 50). Each of these three phenotypic categories comprises an enormous and growing range of phenotypes. For example, autoinflammation encompasses conditions as diverse as type I interferonopathies and the excessive production of interleukin (IL)-1β (51–54). The genetic analysis of immunological dysregulation has led to genetic conclusions, in terms of the genetic architecture of clinical phenotypes, similar to those in the field of infectious diseases. The idea has emerged that a severe clinical phenotype related to infection, (virus-driven) cancer, allergy, autoimmunity, or autoinflammation may be due, at the population level, to rare variants with a strong impact, with individual patients having monogenic lesions displaying high-level but seldom complete penetrance. In other words, there is often genetic heterogeneity but physiological homogeneity (9). Again, type I interferonopathies neatly illustrate this notion (51, 54). The genetic dissection of IEIs other than those underlying infections has had a considerable immunological and clinical impact, but a detailed consideration of these IEIs lies beyond the scope of this review.

The Pathogenesis of Infectious Diseases Inferred from Primary Immunodeficiencies

Studies of PIDs can be used to decipher the mechanisms of immunity to infections in natural conditions (55, 56). This approach also provides unique insight into the mechanisms of disease in patients without IEIs (e.g., patients infected with human immunodeficiency virus) (57). Many PIDs affect the core antigen-specific reactivity of adaptive immunity, either directly, through an impact on T or B cells, or indirectly, by modifying the development or function of subsets of antigen-presenting myeloid cells. This is consistent with the diversity and recurrence of the infectious phenotype, because both the capacity to recognize a broad range of microbial antigens and immunological memory are disrupted. The severity of these infections, some of which are caused by weakly pathogenic microbes, also illustrates the key role played by adaptive immunity. Many PIDs impair both innate and adaptive leukocytes, and sometimes other cell types too, as reported for *NEMO* mutations (23, 58). Some PIDs, such as severe congenital neutropenia, selectively affect innate leukocytes, elegantly revealing the essential and redundant roles of these cells in host defense (25, 59). We have also recently observed an increase in the number of PIDs affecting predominantly innate (leukocytic) or intrinsic (nonleukocytic) immunity. Collectively, the infections seen in patients with PIDs suggest a role for specific cell subsets or molecular pathways in host defense against a particular type of pathogens. It is, therefore, possible to infer general mechanisms of protective immunity from the list of IEIs underlying any given infection. Due to space constraints, we cannot review here all the many human pathogens, and previous reviews have dealt with PIDs disrupting immunity to mycobacteria (60, 61), pneumococcus (62), herpes simplex virus 1 (HSV-1) (63), Epstein–Barr virus (EBV) (64), human papillomaviruses (HPVs) (65), and *Candida* (66). As an example, studies of the considerable genetic diversity of PIDs underlying invasive pneumococcal disease revealed a common immunological mechanism. The opsonization of pneumococci by antibodies (Abs) or complement as well as their destruction by splenic macrophages constitute the essential mechanism of antipneumococcal immunity (62, 67).

An Immunological Lesson from Primary Immunodeficiencies: Redundancy

PIDs have taught us that severe infections can be genetic and that a given infection can be favored by various genetic deficiencies, which are often immunologically related (9). The other side of the coin is that PIDs have also provided evidence that many genes, even those governing the development of normally abundant leukocyte subsets, display surprisingly high levels of redundancy in host defense, as inferred from the infections not seen in patients with the corresponding deficiency (25). This aspect was uncertain when only a few patients had been studied, but it has become increasingly well established with studies of large numbers of patients of diverse ancestries living in various environments. For example, humans without B cells can normally control the vast majority of common viruses, at least in countries with sufficient medical care for the diagnosis of such patients. Patients without autologous T cells suffer from a much broader range of infections, but nevertheless appear to be able to fend off a surprising number of common pathogens, such as HSV in the brain and influenza virus in the lungs. Reviewing the infections observed in patients lacking other leukocyte subsets or their functions, or combinations of subsets, would go beyond the scope of this article. Suffice it to say that the genetic etiologies of PIDs have provided unique insight into the redundancy of specific cell types or molecular circuits, when PID-causing genes and their immunological consequences are considered one by one. The genes underlying PIDs display low redundancy relative to those underlying Mendelian or monogenic infections, discussed below, which display high redundancy (25). However, comparisons with mouse models in this respect are already of interest, as there is much greater redundancy even in humans with PIDs infected in natural conditions than in the corresponding mutant inbred mice infected in experimental conditions (25, 68–71).

Identification of the Genetic Lesions Underlying Primary Immunodeficiencies

It was the identification of molecular genetic lesions underlying PIDs that provided definitive proof that infections can be genetic. It has been known since 1952 that a lack of Ig at birth underlies recurrent, invasive pneumococcal disease and that Abs are, therefore, required for protective immunity to pneumococcus (26–28). Studies of familial cases strongly suggested that agammaglobulinemia could be inherited as an XR trait, but this was not conclusively proven until the identification of *BTK* mutations in 1993 (72, 73). We do not have the space here to review all the discoveries of the molecular basis of PIDs to date. Key milestones included the discovery of the first mutated PID gene, *ADA*, in 1985 (74) and the discovery, by positional cloning, of *CYBB* in 1986 (75). The annual rate of discovery of PID genes is steadily increasing. These PIDs have provided proof of principle not only that rare, opportunistic infections can be genetic (e.g., *Pneumocystis* pneumonitis) but also that more common infections can be genetic, because patients with these PIDs often suffer from such infections (e.g., invasive pneumococcal disease). Some children with PIDs conferring predispositions to various infections die from a single infection, occasionally also after a late onset, that mimics Mendelian or monogenic infections. For example, children can die in the course of a first episode of invasive pneumococcal disease due to T cell deficiency (which would have predisposed them to other infections had they survived) or IRAK-4 deficiency (which would have predisposed them to recurrences, and perhaps to staphylococcal disease, had they survived) (76). It is difficult to overestimate the historical importance of PIDs in the development of the genetic theory of infectious diseases. These conditions have provided proof of principle that severe infectious diseases can be due to IEIs (8, 21), not only in children with multiple, recurrent, rare infections but also in children who die from their first common infection.

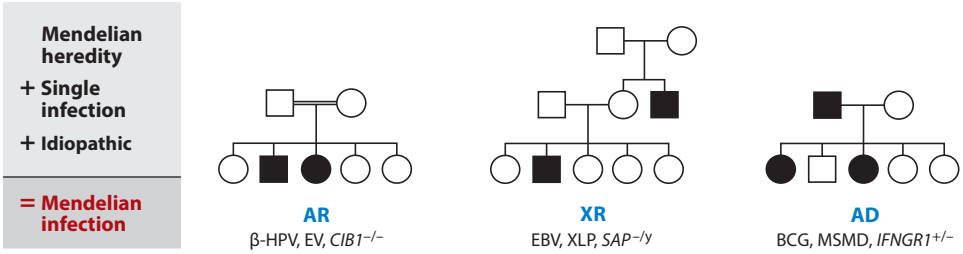

Figure 2

Pedigrees for Mendelian infections, for the three modes of inheritance: autosomal recessive (AR), with the example of epidermodysplasia verruciformis (EV) following β–human papillomavirus (β-HPV) infection due to CIB1 deficiency (the double line indicates that the parents are consanguineous); X-linked recessive (XR), with the example of X-lymphoproliferative disease (XLP) following Epstein–Barr virus (EBV) infection due to SAP deficiency; and autosomal dominant (AD), with the example of Mendelian susceptibility to mycobacterial disease (MSMD) following BCG infection due to interferon (IFN)-γR1 deficiency. Mendelian infections are typically characterized by severe, idiopathic infection with a single, rare pathogen; the absence of classic immunological abnormalities; and a high penetrance (see **Table 1**). Squares indicate males, circles indicate females, filled shapes indicate affected individuals, and unfilled shapes indicate unaffected individuals.

STEP TWO: MENDELIAN INFECTIONS

Idiopathic and Mendelian Infections

Mendelian inheritance characterizes a handful of infectious diseases that are very rare relative to the large number of infected individuals who remain asymptomatic (e.g., clinical disease caused by weakly virulent BCG vaccines or environmental mycobacteria) (**Table 1**) (**Figure 2**). This contrasts with the deceptively "Mendelian" occurrence of more common infectious diseases caused by more virulent microbes, which merely coincidentally reflect intrafamilial contagion (e.g., TB, caused by the more virulent *Mycobacterium tuberculosis*). The former were long considered idiopathic because the lack of an associated immunological abnormality left their pathogenesis unclear. Their frequent familial occurrence, with segregation resembling that of a Mendelian trait, raised the possibility of a genetic etiology. A remarkable feature of these purportedly idiopathic but Mendelian infections is that they strike otherwise healthy individuals with normal resistance to other infectious agents. The five known idiopathic Mendelian infections are (*a*) EV, which was known by 1946 to be an AR predisposition to cutaneous disease caused by viruses (32) identified in 1978 as β-HPVs (77); (*b*) Mendelian susceptibility to mycobacterial disease (MSMD), an AR, AD, or XR predisposition to BCG vaccines and environmental mycobacteria, known since 1951 (60, 78); (*c*) invasive dermatophytic disease, an AR predisposition to severe disease caused by dermatophytic fungi, known since 1957 (79, 80); (*d*) XR lymphoproliferation and related diseases caused by EBV, which were described from 1974 onward (81, 82); and (*e*) chronic mucocutaneous candidiasis (CMC), an AR or AD condition marked by cutaneous and mucosal lesions due to the fungus *Candida albicans*, described from 1967 onward (80, 83). Four of these five groups of infectious agents infect almost all humans, typically without clinical consequences, and the remaining agent, EBV, infects more than 90% of individuals worldwide, typically causing self-healing infectious mononucleosis (84). Four of these five infectious diseases have also been described as opportunistic in other patients vulnerable to other infections, whereas invasive dermatophytic disease appears to be always isolated and idiopathic.

Epidermodysplasia Verruciformis

Starting in 1946, EV has been shown to be an AR predisposition to skin-tropic β-HPVs causing flat warts, pityriasis-like lesions, and nonmelanoma skin cancer (32, 85). Keratinocytes are the exclusive hosts of these viruses. The β-HPVs concerned are E5- and E8-deficient viruses, accounting for the lack of clinical manifestations in the general population (85). In its typical form, EV is isolated, with patients developing skin lesions only, beginning in the first 2 decades of life and persisting or recurring throughout the patients' lifetime. We do not discuss here the opportunistic forms of EV seen in patients with T cell PIDs before or after hematopoietic stem cell transplantation (86–88). Three genes, *TMC6*, *TMC8*, and *CIB1*, encoding EVER1, EVER2, and CIB1, respectively, are mutated in approximately 75% of patients with typical EV (89, 90). These genetic defects were discovered by genome-wide approaches beginning in 2002. The products of these genes form a complex in the cytoplasm of keratinocytes, as CIB1 is degraded in EVER-deficient cells (89). This complex probably operates as a restriction factor that can be overcome by HPVs encoding the E5 or E8 virulence factors, which interact with CIB1. Defective β-HPVs, lacking E5 or E8, may therefore cause disease only in rare individuals with genetic defects causing a lack of the EVER–CIB1 restriction factor. The first IEI to be described clinically, EV, was not added to the list of known IEIs until 2004, because there was no immunological abnormality associated with these idiopathic β-HPV-driven lesions (21). Even now, in 2020, most immunologists do not consider keratinocytes to be immunological cells (23). EV may have provided the first evidence that nonhematopoietic, cell-intrinsic immunity to viruses can be life-saving (23). Interestingly, the EVER–CIB1 complex is not controlled by type I and III interferons (IFNs), consistent with the lack of β-HPV-driven lesions in patients with inborn errors of these IFNs (91–94). The study of EV also provided the first evidence of the oncogenicity of HPVs, before the implication of these viruses in cervical cancer (85). Very few conditions have contributed so much to biomedical knowledge.

X-Lymphoproliferative Disease and Other Inborn Errors of Immunity to Epstein–Barr Virus

X-lymphoproliferative disease is another viral disease that can strike otherwise healthy patients upon primary infection. Initially described in the 1970s, this condition manifests as hemophagocytosis during the course of EBV infection, or as hypogammaglobulinemia or B cell lymphoma at later time points (81, 82). The EBV causing XLP is of similar virulence to the EBV strains causing infection in the general population. The first family described clearly displayed XR inheritance, a finding subsequently confirmed by numerous reports. Patients have no particular clinical history before they encounter the virus. No immunological abnormality has been found in affected male patients diagnosed before EBV infection since the discovery of the causal gene, *SAP*, in 1998 (95–97). As the three postinfection phenotypes involved leukocytes, each in its own way, and despite the absence of an immunological phenotype before EBV infection, XLP was soon considered to be an IEI. The discovery of *SAP* defects by genome-wide approaches led to the recognition that *SAP*-expressing $CD8^+$ T cells were crucial for the control of EBV-infected B cells (98, 99). This line of research turned out to be extremely fruitful. *XIAP* mutations found in other families presenting XR inheritance can also be pathogenic in the absence of EBV infection, through a different mechanism disrupting B cell apoptosis (64, 100). AR deficiencies of CD27 (101), CD70 (102, 103), and ITK (104), which are more closely related to XR SAP deficiency, also underlie severe EBV disease in otherwise healthy patients. Two of these gene products, CD27 and CD70, interact with each other, CD27 being expressed on the surface of B cells and CD70 on that of $CD8^+$ T cells. ITK operates within T cells, downstream from CD70. These discoveries have shown that isolated,

life-threatening EBV disease in otherwise healthy patients can be genetic. They have also revealed a key molecular mechanism by which human T cells control EBV-infected B cells, while suggesting that the SAP–CD70–CD27–ITK circuit is otherwise largely redundant in host defense.

Mendelian Susceptibility to Mycobacterial Disease

The most thoroughly characterized Mendelian infection is caused by weakly pathogenic species of the *Mycobacterium* genus. The first cases of unexplained disease caused by the BCG vaccine in otherwise healthy children were probably reported in 1951 (105, 106). Affected patients are also vulnerable to environmental mycobacteria. As idiopathic BCG-osis and mycobacteriosis are often familial, with AR, AD, or XR modes of inheritance, this condition was designated MSMD (60). However, the patients are also susceptible to a few other intramacrophagic pathogens, such as *Salmonella* (107). Since 1996, MSMD-causing mutations have been found in various genes encoding proteins involved in the control of IFN-γ immunity (78, 108–111). Some of these genetic defects impair the production of IFN-γ, whereas others impair the response to this cytokine. The IFN-γ response pathway is crucial in mononuclear phagocytes, but the cellular basis of MSMD in poor producers of IFN-γ is unclear, as many innate and adaptive lymphocyte subsets can produce this cytokine (112–114). These findings have had important clinical implications. They have made it possible to obtain a genetic diagnosis, to provide genetic counseling, and to prevent or treat disease on the basis of an understanding of its pathogenesis, with injections of IFN-γ in patients with at least a residual IFN-γ response pathway and hematopoietic stem cell transplantation in patients in whom cellular responses to IFN-γ are completely abolished (78, 115, 116). These findings also suggest that so-called opportunistic mycobacterial disease in patients with other deficits, whether inherited or acquired, probably results from inadequate IFN-γ immunity. Immunologically, these findings show that IFN-γ acts less as an antiviral IFN and more as a macrophage-activating factor (117). Moreover, IFN-γ appears to be largely redundant for host defense against most intracellular microbes, despite its role as the Th1 signature cytokine in mice (118). This high level of redundancy remains surprising, perhaps more so than for host genes with mutations underlying β-HPV or EBV disease, if only because of the extensive studies of IFN-γ immunity in mice (69).

Chronic Mucocutaneous Candidiasis

Since 1969, a few patients have been reported to suffer from idiopathic CMC, segregating as an AD or AR trait (119, 120). CMC is defined as persistent or recurrent infection of the skin and nails, and oral, esophageal, and genital mucosae, by fungi of the genus *Candida* (121). It has long been known to occur in patients with acquired or inherited forms of $CD4^+$ T cell deficiency, who display multiple infections (121). By contrast, inherited forms of purportedly idiopathic CMC were typically thought to be isolated, although some patients also had staphylococcal lesions of the skin. Studies performed since 2011 have shown that some patients with isolated CMC carry mutations of the gene encoding IL-17F (which can form multimers with IL-17A) or its response pathway, with mutations affecting IL-17RA, IL-17RC, ACT1, or JNK1 (121–125). These discoveries were driven by previous studies identifying *STAT3* mutations in a syndromic form of CMC known as HIES, and the identification of auto-Abs directed against IL-17A/F in patients with a monogenic form of autoimmunity with CMC (66, 126, 127). Three other, related forms of syndromic CMC were subsequently reported, due to biallelic loss-of-function mutations of *RORC* (128) or *ZNF341* (129) and monoallelic gain-of-function mutations of *STAT1* (130). Overall, the emerging picture is one of IL-17A/F-dependent immunity mediated by IL-17RA/RC being essential for protective mucocutaneous immunity to *Candida albicans* (and, to a lesser extent, *Staphylococcus aureus*), but

otherwise redundant in host defense. The cellular basis of CMC in these patients remains unclear, as multiple subsets of innate and adaptive lymphocytes can normally produce IL-17A/F, and many nonhematopoietic cell types respond to these cytokines. These studies revealed that Th17 immunity plays a narrower role in humans infected in natural conditions than in inbred mice challenged by experimental infections (68). These studies also suggest that CMC results from impaired IL-17A/F immunity in patients with human immunodeficiency virus infection or other T cell deficiencies.

Invasive Dermatophytic Disease

The fifth and last Mendelian infection considered here is another cutaneous and fungal infection, at least in the early stages of disease. Dermatophytes are fungi that often cause benign, cutaneous infections; in very rare cases, as first reported in 1957, they cause invasive disease, reaching deep organs such as the bones, liver, and brain (79, 80). Such invasive diseases are not seen in patients with PIDs and multiple infections. These fungi have not been reported to be opportunistic. They paradoxically strike otherwise healthy patients, who can reach the age of 70 after decades of severe disease caused by one specific microorganism while displaying normal resistance to countless other infectious agents. All patients with invasive dermatophytic disease studied carry biallelic mutations of *CARD9* (80, 131, 132). Thus, this is the only example of genetic homogeneity among the five Mendelian infections. Perhaps partly for this reason, the immunological mechanism underlying invasive dermatophytic disease remains unclear, but it is thought to involve the CARD9-dependent responses of phagocytes to the engagement of their receptors by fungi (133). It also remains unclear whether all mutations are loss of function and whether they affect all CARD9-dependent pathways equally. Remarkably, many other CARD9-deficient patients have been reported to present with invasive diseases caused by other fungi, including *Candida*, *Aspergillus*, *Phialophora*, *Exophiala*, *Corynespora*, *Aureobasidium*, and *Ochroconis*, all of which belong to the phylum Ascomycota (133, 134). Surprisingly, some patients experience their first clinical manifestations late in adulthood, with an entirely unexpected severe fungal infection caused by a common fungus. Intriguingly, each CARD9-deficient patient develops a single fungal disease. The mechanisms governing the nature of the fungal infection do not seem to depend on *CARD9* genotype. The search for the cellular and molecular basis of invasive dermatophytic disease and other fungal diseases in CARD9-deficient patients should yield novel immunological and clinical insights.

Lessons from Mendelian Infections

The very small group of Mendelian infections has played a crucial role in the history of this field, providing chronological and intellectual bridges to two much larger groups of conditions: (*a*) the PIDs first described clinically in the 1950s and molecularly from 1985 onward and (*b*) the monogenic infections first described clinically and molecularly as such from 2007 onward. The disease-causing genes for the few infections known to segregate as Mendelian traits in some families from 1946 onward were discovered beginning in 1996, attracting more attention to these conditions. These five infections were, thus, no longer "idiopathic." Their Mendelian inheritance had a molecular basis, in turn pointing to an immunological mechanism. The infectious manifestations were seen as a phenotype, and this approach elegantly led to the discovery of a genotype, in turn facilitating the dissection of a molecular, cellular, and immunological mechanism. With the benefit of hindsight, these five Mendelian infections are reminiscent of inborn errors of the terminal components of complement, which selectively underlie meningococcal disease and were characterized clinically and immunologically in the 1970s, with their genetic lesions discovered

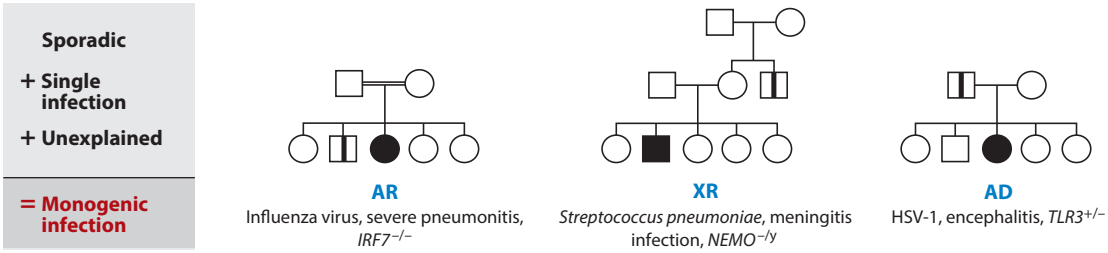

Figure 3

Pedigrees for monogenic infections, for the three modes of inheritance: autosomal recessive (AR), with the example of severe influenza pneumonitis due to IRF7 deficiency (the double line indicates that the parents are consanguineous); X-linked recessive (XR), with the example of invasive pneumococcal infection due to NEMO deficiency; and autosomal dominant (AD), with the example of herpes simplex virus 1 (HSV-1) encephalitis due to TLR3 deficiency. Monogenic infections are characterized by severe, unexplained infection with a single, common pathogen; the absence of classic immunological abnormalities; and a low penetrance. Vertical bars indicate healthy carriers of the deleterious genotype (see **Table 1**). Squares indicate males, circles indicate females, filled shapes indicate affected individuals, and unfilled shapes indicate unaffected individuals.

2 decades later (21, 135). These disorders did not usher in an era of research into the genetic basis of isolated infections, because their discovery did not follow the testing of the hypothesis that meningococcal disease could have a monogenic basis (8, 21). The five Mendelian infections reviewed here proved, beyond any reasonable doubt, that a human could be highly, selectively, and genetically vulnerable to a single infectious agent, over the course of an entire lifetime, while successfully fending off countless other pathogens. Admittedly, only five such Mendelian infections have been identified, and they are all relatively rare. Nevertheless, they paved the way for a paradigm shift leading to the discovery of infections that were monogenic but not Mendelian.

STEP THREE: MONOGENIC INFECTIONS

From BCG-osis to Tuberculosis

Could isolated, severe rare or common infections be monogenic, at least in some patients (**Figure 3**)? As severe infections are more often sporadic than familial, and familial infections may reflect contagion, the underlying monogenic lesions, if any, were predicted to display incomplete penetrance (9, 21). What actually led to the testing of this idea was the discovery of Mendelian infections and, in particular, the study of MSMD. The first step was the demonstration that AR IL-12Rβ1 deficiency displayed incomplete penetrance for the case-definition phenotype of MSMD (136, 137). Affected patients develop MSMD because the IL-12- and IL-23-dependent induction of IFN-γ is abolished. This surprising and unexplained observation, implying that MSMD is a misnomer for some of its etiologies, led to the discovery that some of these patients had retained vulnerability to the more virulent *Mycobacterium tuberculosis* (136, 137). Some children, adolescents, and even young adults with IL-12Rβ1 deficiency developed TB as their sole clinical phenotype (138–143). As IL-12Rβ1 deficiency is rare, found in no more than 1 in 500,000 births, it cannot be a common cause of human TB (140). AR TYK2 deficiency is another rare genetic etiology of MSMD, with incomplete penetrance, that also impairs the IL-12- and IL-23-dependent induction of IFN-γ and can underlie TB (144). We recently found particularly high levels of homozygosity for a common variant of TYK2 (P1104A) both in a heterogeneous cohort of TB patients from non-European countries endemic for TB (112) and in the large European UK Biobank cohort (145). This variant, P1104A, is homozygous in ∼1 in

600 Europeans and ~1 in 2,500 people from other countries outside East Asia and sub-Saharan Africa. Homozygosity for P1104A is associated with a selective impairment of IL-23-dependent IFN-γ production (112). This genetic condition displays low penetrance for MSMD, like IL-23R deficiency (114), but high penetrance for TB (at least 50%) in endemic areas and appears to be responsible for approximately 1% of TB cases in populations of European descent. It is the first common monogenic cause of TB to be described. The study of BCG-osis has thus led to the discovery of both rare and common monogenic etiologies of TB.

Invasive Pyogenic Bacterial Disease

The study of invasive pneumococcal disease provided a second example of a relatively common infection that turned out to be monogenic in some cases. Pneumococcus (*Streptococcus pneumoniae*) is a bacterium that infects almost all humans but causes life-threatening, invasive disease only rarely (67). Known genetic etiologies include disorders of the phagocytosis of opsonized bacteria by splenic macrophages (62, 67). Patients with such defects are prone to multiple infections (PIDs), with the exception of those with isolated congenital asplenia, half of whom carry mutations causing haploinsufficiency at the *RPSA* locus (146, 147). Studies of children with a classic PID—XR anhidrotic ectodermal dysplasia with immunodeficiency (148–150)—led to the discovery of mutations of *NEMO*, which in turn led to the discovery of AR IRAK-4 and MyD88 deficiencies in patients with idiopathic pneumococcal disease, often associated with staphylococcal disease (151, 152). Patients with MyD88 or IRAK-4 deficiencies do not respond to Toll-like receptor (TLR) agonists (except TLR3), IL-1, IL-18, IL-33, or related cytokines. Remarkably, they suffer from invasive bacterial disease caused by pneumococcus and/or, more rarely, *Staphylococcus aureus* (67). The molecular pathogenesis of their pneumococcal disease remains unclear, but AR TIRAP deficiency, which selectively impairs the TLR2- and TLR4-dependent activation of nuclear factor κB, can underlie invasive staphylococcal disease (153). One index case had staphylococcal disease due to an impairment of TLR2-dependent responses to staphylococcal lipoteichoic acid (LTA). However, in seven healthy relatives, this genetic defect remained clinically silent, due to the rescue of TLR2-dependent LTA recognition by circulating Abs against LTA. The index case developed no such Abs. An inborn error of TLR2 innate immunity to LTA is, therefore, rescued by adaptive Abs against LTA. Incomplete penetrance for staphylococcal disease in this kindred is explained not by germline modifiers but by somatic, adaptive, immunological events. Overall, studies of congenital asplenia and of the TLR pathway have also suggested that monogenic but not Mendelian disorders can underlie isolated staphylococcal or pneumococcal disease.

Herpes Simplex Encephalitis

The question arose as to whether infections that are almost never opportunistic and almost always sporadic could be caused by monogenic lesions (**Table 1**). The first advance was made in 2007, with genetic studies of HSV-1 encephalitis (HSE) (154, 155). Patients with HSE generally develop this disease during primary infection with HSV-1, and are not particularly susceptible to any other infectious disease. This infection is neurotropic, both in terms of the end destination, the central nervous system (CNS), and in terms of the route, with the virus reaching the CNS via the olfactory (to the forebrain) or trigeminal nerves (to the brainstem) (156, 157). We discovered inborn errors of TLR3-mediated and IFN-α/β- and IFN-λ-dependent immunity, which includes six forebrain HSE-causing genes (154–156, 158–162). Inherited TLR3 deficiency, which was discovered in 2007, displayed incomplete penetrance, unlike UNC93B deficiency, discovered 1 year earlier (154, 155). Subsequent studies showed that induced pluripotent stem cell (iPSC)-derived

cortical neurons from the patients displayed impaired CNS cell-intrinsic immunity to HSV-1, whereas their trigeminal neurons were not affected by TLR3 deficiency (163, 164). Moreover, the TLR3 pathway is redundant in leukocytes, accounting for the lack of dissemination of HSV-1 in the course of HSE (163). AD SNORA31 deficiency underlies forebrain HSE by mechanisms other than disruption of the TLR3 pathway (165). Collectively, these data suggested that childhood HSE could result from a diverse collection of CNS-intrinsic monogenic IEIs. The mechanisms of incomplete penetrance are unknown. Finally, a severe incomplete form of AR DBR1 deficiency impairs RNA lariat debranching and underlies brainstem infection by at least three unrelated viruses, including HSV-1 and influenza virus (166). Cell-intrinsic immunity in fibroblasts is impaired, suggesting that the mechanism of disease also involves brainstem cell-intrinsic processes. This experiment of nature surprisingly connected an RNA metabolism housekeeping gene with viral infections within a very narrow anatomical territory in the CNS. Overall, the study of viral encephalitis has revealed the importance of CNS-intrinsic immunity to viruses (23). These findings also provided proof of principle that sporadic, nonopportunistic infections can be caused by single-gene IEIs.

Severe Influenza Pneumonitis

Having discovered the first genetic basis of HSE, and a genetic basis of brainstem influenza, we turned our attention to another relatively common viral disease, severe influenza pneumonitis (167). We hypothesized that life-threatening influenza pneumonitis striking otherwise healthy humans might result from a single-gene IEI. We first discovered an AR deficiency of IRF7, a transcription factor that amplifies the production of antiviral IFN-α/β and IFN-λ in both circulating plasmacytoid dendritic cells and iPSC-derived pulmonary epithelial cells (168). AD GATA2 deficiency, which impairs the development of plasmacytoid dendritic cells, is perhaps the only PID that can underlie severe influenza pneumonitis in the context of other infections (167, 169). The study of IRF7 deficiency paved the way for the discovery of AR IRF9 deficiency in a child with severe influenza (170). The patient's cells did not form STAT1–STAT2–IRF9 trimers, known as ISGF3, in response to stimulation with IFN-α/β or IFN-λ. The penetrance of IRF7 and IRF9 deficiencies cannot be estimated from these families, as both conditions were found in single patients. However, penetrance is probably incomplete, as another IRF9-deficient patient was subsequently reported to suffer from other viral infections (171). It is unclear whether AR defects of IFNAR1, IFNAR2, and STAT2 have not been implicated in severe influenza because of incomplete penetrance (in which case the description of more patients would reveal such cases) or because of the occurrence of compensatory mechanisms (e.g., the integrity of type III IFN in patients with *IFNAR1* or *IFNAR2* mutations) (91, 93, 167, 172). Finally, *TLR3* mutations have also been found in patients with severe influenza pneumonitis, including the *P554S* variant, which has been reported in several patients with HSE (173). The mechanism of disease probably involves an impairment of the production of antiviral IFNs in pulmonary epithelial cells. HSE and influenza pneumonitis are, therefore, two severe infections that may be considered allelic at the *TLR3* locus, with incomplete penetrance for both phenotypes accounting for the absence or rarity of dual infections.

Other Monogenic Infections

There are several infectious diseases for which only one genetic etiology has been discovered, often in a single patient. After showing that Kaposi sarcoma can occur in children with certain PIDs and multiple infections (174–177), we identified AR OX40 deficiency as the first genetic etiology of isolated, idiopathic Kaposi sarcoma (178). Other examples of single-gene infections

include AR NLRP1 gain of function in patients with laryngeal HPV disease (179); AR IL-18BP deficiency in a patient with fulminant viral hepatitis (180); AR NOS2 deficiency in an adult with lethal cytomegalovirus primary infection at the age of 50 years (181); AR APOL1 deficiency in a patient with trypanosomiasis caused by a weakly virulent species (182); AR MDA5 deficiency in a patient with severe respiratory viral illnesses, caused by rhinovirus in particular (183), and *MDA5* mutations in patients with other severe respiratory viral infections, caused by respiratory syncytial virus in particular (184); AD combined POLR3A and POLR3C deficiencies in patients with varicella zoster virus encephalitis (185); AD IRF4 deficiency in patients with Whipple's disease due to *Tropheryma whipplei* (186); and AR IFNAR1, IFNAR2, or STAT2 deficiency in patients with isolated measles or yellow fever vaccine disease (91, 93, 172, 187). The molecular and cellular bases of disease in these patients are beyond the scope of this review, but the studies concerned provided ample evidence that life-threatening diseases striking otherwise healthy individuals with no relevant familial history in the course of primary infection, which cannot be explained by an overt comorbid condition, may be caused by a single-gene IEI. The penetrance of most of these disorders is unknown but is predicted to be typically incomplete (although exceptions are possible).

From Mendelian to Monogenic Infections and Back Again

It has long been known that some rare or even common infections can occur as the first and, sometimes, the last clinical manifestation in patients with PIDs. Such patients may die during this first infection, or be diagnosed and managed appropriately, which would be sufficient to mask the otherwise inevitable development of other infections. This alone could have been sufficient to spark the idea that sporadic, isolated infections, whether rare or common, and particularly those that are opportunistic in other patients, may also have a monogenic basis, but it did not. Even the more directly relevant observation that inborn errors of the terminal components of complement can underlie isolated meningococcal disease did not cause the connection to be made. These observations were reported, but not fully understood. The five Mendelian infections considered here opened up new horizons. Interestingly, monogenic infections other than these five Mendelian infections are not always non-Mendelian, as they can show complete penetrance in some kindreds. Conversely, the five Mendelian infections can also present as sporadic infections, for various reasons, such as their occurrence in a single child (for recessive traits) or because a causal variant is de novo (for recessive and dominant traits). Moreover, some genetic etiologies of the five Mendelian infections do not display complete penetrance. For example, AR IFN-γR1 deficiency displays complete penetrance for MSMD by the age of 5 years, whereas AR IL-12Rβ1 deficiency displays only 50% penetrance in adults, and homozygosity for TYK2 P1104A has a penetrance of less than 5% (112, 136, 137, 145, 188). In some families, both sporadic and familial, rare or common, severe, isolated infections may be caused by Mendelian or non-Mendelian monogenic IEIs. The classification of IEIs as Mendelian or non-Mendelian monogenic derives from their study at the population level, with most monogenic disorders probably showing incomplete penetrance in most but not all affected families.

Genetic Heterogeneity and Physiological Homogeneity

Different infectious diseases can be allelic at the same human locus. Different defects at the same locus may govern different infections, via different mechanisms. A good example is provided by *STAT1*, gain-of-function heterozygous mutations of which can underlie fungal infections (because of impaired IL-17 immunity), while loss-of-function heterozygous mutations can underlie mycobacterial infections (because of impaired IFN-γ immunity) (130, 189, 190). Alternatively, two infections can be favored by the same disorder and mechanism, and even the same genotype, as

exemplified by HSE and influenza pneumonitis, both of which can be driven by AD TLR3 deficiency and even heterozygosity for the *P554S* allele (155, 173). In this case, incomplete penetrance accounts for the very rare overlap of the two infections in the same patient (191). Notwithstanding the genetic intersection between some infections (one locus, multiple infections), it is important to emphasize the apparently high level of genetic heterogeneity underlying the few severe infectious diseases studied to date (one infection, multiple loci). For example, there are already 31 genetic etiologies of MSMD, encompassing mutations of 16 genes (60, 78, 108, 109). This is understandable, as an enormous number of different cells are encountered by the pathogen between its first contact with the host and the host's death. Another example is provided by the genetic heterogeneity of invasive pneumococcal disease, which is high among both PIDs and monogenic infections. However, children with isolated pneumococcal disease or isolated congenital asplenia display a high level of genetic homogeneity (67, 146, 147). For patients with MSMD or invasive pneumococcal disease, however, the genetic heterogeneity does not mask an equally high level of physiological homogeneity. All genetic etiologies of MSMD disrupt IFN-γ immunity, whereas all known genetic etiologies of pneumococcal disease impair the splenic phagocytosis of opsonized bacteria. Collectively, these findings suggest that life-threatening infectious diseases can each result from a collection of highly diverse and incompletely penetrant monogenic IEIs that are physiologically connected (9).

CONCLUDING REMARKS

Human Genetic Architecture of Severe Infectious Diseases

If many or most severe infectious diseases of humans manifested as Mendelian traits, their genetic origin would have been discovered long ago. If only they were much more often familial than sporadic, their genetic origin would at least have been suspected, although familial clustering would probably have been attributed to contagion. Their sporadic nature, in the genetic sense of the term, together with their known environmental cause, the microbe, formed formidable obstacles to the conception of a hypothetical genetic architecture that would be both plausible and testable, and to the development of a rigorous experimental approach for testing this model. Severe infectious diseases were shown to contribute to the selection of alleles conferring resistance, as best illustrated by the spread of sickle cell hemoglobin regions in which *Plasmodium falciparum* is endemic, for which candidate and genome-wide association studies based on common variants were unable to explain the human genetic basis of the severe infections tested (8, 145). Death from infection is, indeed, an extreme phenotype, and the one that really matters evolutionarily, particularly if it occurs before or during the reproductive years (192). This led to consideration of the idea that severe infections might be caused by monogenic lesions (21). The study of a handful of Mendelian infections connected the genetic study of PIDs with that of sporadic, isolated, idiopathic infections. A small but growing range of diseases that are life-threatening in the course of primary infection and caused by various viruses, bacteria, fungi, and parasites, in otherwise healthy children, adolescents, and adults, have been shown to be caused by monogenic IEIs, mostly with incomplete penetrance (9, 10). Obviously, we are only beginning to unravel the human genetic architecture of severe infectious diseases.

Upcoming Challenges

Only a very small minority of severe infectious diseases are currently explained by monogenic lesions, and only for a very small proportion of cases. Two exceptions are MSMD, which is understood in approximately half of patients, and HSE, which is understood in approximately 5%

of cases (9, 78, 156). There are probably novel forms of acquired immunodeficiency to be discovered, associated with aging, for example (8, 21, 193). However, the pursuit of the human genetic study of severe infectious diseases aims to establish a new paradigm. A genetic theory of infectious diseases requires a human genetic architecture of severe infectious diseases. In the jigsaw puzzle of the genetic basis of severe infections, only a very small number of pieces have been assembled as yet, and only a few of them are contiguous. An enormous amount of work lies ahead. At the moment, it seems that we can find monogenic lesions for almost any life-threatening infection studied in humans. As a first step, we will need to test all infections, one by one. Second, we will need to determine the proportion of life-threatening cases that are monogenic, infection by infection. This is a daunting task, even for an entire generation of scholars. Third, we will need to analyze the molecular and cellular mechanisms of incomplete penetrance (9, 191). Epistasis may be involved, and digenic immunodeficiencies may underlie some infections. Somatic genetics may also be crucial, as shown for TIRAP deficiency (153). The environment itself, through the number of invading pathogens, for example, may influence clinical penetrance (191). These three steps will probably be undertaken in parallel. They will hopefully take us to the summit, that is, to a full understanding of the root cause of severe human infectious diseases. The outlook is certainly worth the effort. If validated, this theory would reconcile the germ theory and the genetic theory, which have structured physiology and pathology across all living species since 1866 and were thought to be mutually exclusive (8, 11, 21).

Immunological and Medical Implications

The genetic theory of infectious diseases has immunological implications, because it is based on the outcome of primary infection in natural conditions. The genetic studies involved provide an ideal way to define the function of host defense genes *in natura*, that is, in the setting of a natural ecosystem (55, 56). In particular, they have revealed a much greater degree of redundancy in outbred humans in natural conditions of infection than in inbred mice in experimental conditions of infection (25). They have also revealed the importance of cell-intrinsic, nonhematopoietic immunity, scaling immunology up from the immune system to the whole organism (23). The clinical implications of this genetic model are also significant, as emerging pathogens and multidrug-resistant pathogens are posing new and challenging threats to humans. The genetic model allows rigorous molecular diagnosis and genetic counseling, based on the identification of disease-causing genetic lesions of known penetrance in families of diverse ancestries worldwide (194, 195). The prognosis of patients and their personalized treatment and follow-up can also be defined on the basis of the genetic lesion. Perhaps more importantly, these studies pave the way for novel therapies in vulnerable individuals with inborn errors (e.g., cytokine therapy in patients with genetic defects resulting in a deficiency of the cytokine concerned). Prevention or treatment with recombinant cytokines is based on the same principles as those that govern the use of insulin in diabetic patients. Such treatment is already being used, with children worldwide benefiting from treatment with IFN-γ, granulocyte colony–stimulating factor, or other recombinant molecules. The success of the germ theory has been encouraging, but known infectious diseases have remained formidable killers, while new infectious diseases are emerging. In the long term, a full understanding of the pathogenesis of infectious diseases constitutes our best hope of controlling these diseases. The human genetic approach provides a novel path for developing more personalized strategies for preventing and treating infectious diseases. Archibald Garrod's (196) seminal concepts of "inborn errors" and "chemical individuality" may find some of their best applications in the study of the individual genetic determinism of infectious diseases, as a complement to traditional strategies targeting the environmental component of infectious diseases.

Implications for Noninfectious Diseases

The study of IEIs has also led to the discovery of a growing diversity of monogenic and sometimes Mendelian forms of rare autoinflammatory, autoimmune, malignant, and allergic phenotypes (39, 40). More common autoinflammatory and autoimmune conditions may also result from single-gene IEIs. We do not refer here to conditions of the elderly, such as rheumatoid arthritis, but to inflammatory and immunological conditions that strike young individuals and impair reproduction, such as systemic lupus erythematosus. Over the last 2 decades, various human conditions, rare or common, in fields as diverse as cardiology, neurology, gastroenterology, and nephrology, have been shown to be caused by monogenic lesions (197–202). The discoveries of Mendelian and monogenic infections in this context are not exceptional, but their well-known environmental determinism singles them out. Indeed, the human genetic study of severe infectious diseases can be seen as an exemplary study of host–environment interaction in health and disease. One of the strengths of these conditions is that the environmental trigger, the microbe, is much better known than for the vast majority of (if not all) other human conditions. There are other genetic conditions for which clinical expression is also dependent on an environmental trigger, including inborn errors of metabolism, in particular. We know, for example, that the clinical expression of phenylketonuria is dependent on dietary intake of phenylalanine (203). Phenylketonuria and HSE are, thus, similar conditions in that they are intrinsically both genetic and environmental. These similarities raise questions about causality. We classically see phenylketonuria as being caused by tyrosine hydroxylase deficiency. Should we instead consider phenylalanine to be the cause of phenylketonuria, in a manner analogous to the way in which infectious agents are commonly seen in infectious diseases? Or should the human genetic lesions be seen as the cause of infectious diseases? Likewise, are allergens the causes of allergy? Is the peanut truly the cause of a child's death from allergy? The genetic study of immunological conditions, including allergy and infection in particular, will undoubtedly challenge prevailing views about their pathogenesis, and perhaps about human conditions more generally.

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