

Are you immunodeficient?

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In their Rostrum monograph, Casanova et al¹ consider the problems of definition and classification of primary immunodeficiencies (PIs). They begin with a standard and straightforward premise: “immunodeficiency is a failure to achieve immune function to provide efficient, self-limited host defense against the biotic and abiotic environment while preserving tolerance to self.” The challenge to practitioners is to translate this axiom into principles that answer specific clinical and academic needs. One essential message of Casanova et al is to consider the susceptibility to infection limited to one or a few pathogens and having Mendelian inheritance to be within the spectrum of PI, regardless of the immunologic phenotype. They further argue that in light of this, academic and clinical needs will best be met by a classification system on the basis of clinical phenotype, in contrast to the classic, or perhaps traditional, system on the basis of immunologic phenotype.^{2,3} According to their scheme, Casanova et al¹ distinguish conventional and unconventional immunodeficiencies as those that do or do not have clearly defined immunologic phenotypes, respectively. The authors consider these to be end points of a spectrum rather than dichotomous. They further state there has “never been a fully satisfactory classification of PID.” However, it is worth discussing whether any single system on the basis of clinical phenotype or immunologic phenotype could ever be so.

Regardless of how we might classify their diseases, immunodeficient patients come to clinical attention predominantly as a result of a predisposition to infection. This predisposition is manifested in one or more of the clinical dimensions of infection: the inherent virulence of the

Abbreviation used

PI: Primary immunodeficiency

organism, the site of infection (localized vs disseminated), the infection’s severity (degree of tissue or organ damage), the infection’s persistence or resistance to therapy, and the frequency of relapse or reinfection. In spite of the commonality of these considerations early in the approach to the potentially immunodeficient patient, there are very few data or agreement on where to best draw the dividing line between normal and abnormal along any of these dimensions. It might also be important to consider that this line can be drawn differently under circumstances that differ with respect to, for example, the level of public hygiene, the prevalence of particular pathogens, or the availability of vaccinations. (Casanova et al,¹ in fact, consider these factors as masking the true prevalence of PI.) In addition, Casanova et al consider the importance of Mendelian (single gene) inheritance in a clinical definition. Perhaps this element could be generalized to any definable genetic component to include interactions among mutations, polymorphisms, or both that might determine a phenotype, as has been observed in some PI diseases.⁴ Whether one is prepared to alter one’s conceptualization of immune deficiency to include unconventional forms, the matter of definition requires further study from all sides (epidemiology, immunology, and genetics) to provide a more solid framework for further discussion. Ultimately, the issue of where to draw the line between normal and abnormal is critical if the search for “currently unknown Mendelian primary immunodeficiencies”¹ is to set out with hope for meaningful discovery.

The criteria of normalcy in a system based on immunologic phenotype relate to population distributions of screening laboratory studies of immune function (eg, serum immunoglobulin levels and specific antibody titers, peripheral blood lymphocyte subpopulations, *in vivo* or *in vitro* measures of T-cell function, assays of phagocyte oxidative burst or adhesion, and complement function or serum component levels).² This system affords convenient statistical labels for normal and abnormal. Unfortunately, the biologic and clinical correlates are also largely lacking here, as in the discussion of predisposition to infection above. This sometimes leads to an important point raised by Casanova et al¹ that certainly bears repeating: “patients with specific clinical infectious

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diseases but no overt immunological phenotype [are] being largely neglected.”

However, this is not precisely a failure of a system or classification based on immunologic phenotype, as much as it reflects 3 distinct elements. First, one might choose simply not to categorize a limited infection predisposition as a PI, one of the main points of Casanova et al¹ (ie, if it is definable genetically, then we should). Second, we must consider further what is meant by immunologic phenotype. Casanova et al use the adjective “overt” to denote an abnormality detectable by the battery of screening tests listed above. However, at some level, all genetically definable PIs must have some immunologic phenotype; it is the clinical phenotype that dictates the specific evaluation that will ultimately identify it (therefore we can agree on the value of the clinical classification here). And finally, it is clear that we have incomplete knowledge regarding how the organism as a whole (including the immune system) protects itself from infection. Only in recent years have the importance of defects of natural killer cell function⁵ and toll-like receptor signaling^{6,7} become the foci of attention in PI. It is inevitable that the clinical screening immunologic evaluation of patients will continue to develop along with expanding knowledge of immune mechanisms.

In the final analysis, the matter of classification might truly be secondary. Consider Table I, which shows a very simple scheme outlining the biologic and clinical elements of PI and the classification systems that might be proposed in response to or motivated by these different aspects of the interaction of a pathogen with a susceptible host. No system is superior in all cases, and some might even be frankly cumbersome in some situations, but there is no single system that optimally serves all needs.

We all work together toward the determination of complete sets or elements of a PI knowledge base, such as the complete set of gene alterations that lead to susceptibility to infection, the complete set of clinical phenotypes of PIs, and the complete set of immunologic phenotypes. These will not be conveniently ordered along 1 or 2 dimensions that will be useful in every situation, as outlined above. What might serve best is a multisegmented database in which each segment orders the information according to a distinct classification system and every entry is linked to its entries in the other segments. This type of organization is legion on the Internet (see, for example, the National Center for Biotechnology Information of the National Institutes of Health, Bethesda, Maryland, at <http://www.ncbi.nih.gov/>, and the Institute for Medical Technology Bioinformatics Group of the University of Tampere, Tampere, Finland, at <http://bioinf.uta.fi/>).

The adaptive immune system might be dispensable for human development and survival in a germ-free environment.⁸ On the other hand, elements of innate immunity interact with commensal flora and are required for normal function of some systems.⁹ In light of the interrelations of immunity with other organ systems, the boundaries of the immune system, as a whole, become less distinct. Whether

TABLE I. Clinical-academic considerations or questions in PI diseases and potential classification schemes to address them

Biomedical aspects of immunodeficiency	Basis for classification of PI
Infecting microbe(s)	Microbial taxonomy
Host with genetic lesion(s)-polymorphism(s)	Genetic catalog, mode of inheritance
Altered immunopathogenesis of infection	Biochemical and cell biologic mechanisms
Immune dysregulation (atopy, autoimmunity, lymphoproliferation, malignancy)	Biochemical and cell biologic mechanisms
Clinical syndrome of immunodeficiency	All clinical features of the disease
Diagnostic evaluation	Immunologic phenotype
Therapy	Anti-infective, immune reconstitution, response to therapy
Outcome	Natural history, prognosis

it is truly “the least efficient physiological system at the individual level”¹ and whether we might discover that a large fraction of human subjects are immunodeficient depends on one’s perspective, as we have discussed, notwithstanding the benefits of public hygiene, immunization, and antibiotics. This is apparent if one shifts focus from the anthropocentric view and remembers that human pathogens and human beings evolve together.

At the bedside, the clinical immunologist’s interest is piqued by the constellation of history, symptoms, and findings. Some version of the clinical classification of which Casanova et al¹ speak is foremost in our minds while we determine the most efficient path toward defining the immunologic phenotype, making a definitive diagnosis, or both. Experience informs us that our ability to define the immunologic phenotype with precision depends utterly on the sophistication of the laboratory methods available for study of the individual patient. We note in passing that recent advances in molecular methods can, in some instances, divorce the processes of defining the immunologic phenotype from making a diagnosis in the case of a PI that has already been defined at the molecular level. For example, a 15-month-old boy presents with severe recurrent respiratory tract infections with encapsulated bacteria. We sequence his *BTK* gene and find a mutation or deletion consistent with X-linked agammaglobulinemia. We have established a diagnosis without knowing whether he is agammaglobulinemic or B lymphopenic. We do not advocate such an approach, however, because it perpetuates or even creates critical gaps in our knowledge base.

As we stated, the example applies only where the molecular defect is known. The situation is different for the patient with a less well-understood form of PI. The level of laboratory sophistication required for the definition of new forms of PI is an order of magnitude

beyond what suffices for diagnosis of known entities. Technologic advances might soon provide us with the ability to automate functional studies of pathogen-specific immune responses and to link these to genomics-derived strategies to identify loci for study.¹⁰ Wherever they exist, these resources must be made available in some way to the larger community of clinical immunologists. The importance of this cannot be overstated. We agree with Casanova et al¹ that the full spectrum of human susceptibility to infection is largely waiting to be discovered. For those with PI and those who study it, hope derives from a chance encounter with “a prepared mind,” timely recognition, and the technology to repair it.^{11,12}

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