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Chapter 54

Global perspectives on primary immune deficiency diseases

Saul O. Lugo Reyes[a], Antonio Condino-Neto[b,c] and Polina Stepensky[d]

[a]*Immunodeficiencies Research Unit, National Institute of Pediatrics, Mexico City, Mexico;* [b]*Immunology and Experimental Medicine, Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil;* [c]*The Jeffrey Model Center of São Paulo, Sao Paulo, Sao Paulo, Brazil;* [d]*Department of Bone Marrow Transplantation and Cancer Immunotherapy, Hadassah University Hospital, Jerusalem, Israel*

Introduction

Our shrinking planet brings us all into closeness proximity to people of different backgrounds, customs and expectations. Increased travel for leisure, and increasing migration of peoples from dangerous locales, contribute to changes in infectious exposures. To provide responsible medical care, we must recognize exposures, genetic effects and customs that may impact disease manifestations. This chapter will offer global insights into patient management.

Climate change and emerging infectious diseases

The fall of the Roman Empire in the fifth century AD was precipitated by climate change (a little ice age), and emerging infectious diseases (in the form of the first pandemics: smallpox and the bubonic plague).[1] Today, we stand once more at a crucial moment of history, when our fate in this planet may depend on the choices and progress we make during the following decade.

The Earth's population soared from around 1 billion in 1800 to 7 billion in 2010. Global warming has increased steadily during the last century. For the next hundred years we can expect an increase in global temperature of 1.5−5.8 °C[2] together with more winter rain and summer droughts, fewer cold days per year, and other less predictable changes in: wind, humidity, heat waves and extreme weather changes, including hurricanes and floods.

All these climate changes will result in more vector-transmitted diseases in geographical areas where the vectors (mosquitoes, ticks) were previously restricted by temperature or environment (precipitation, elevation from sea level, wind, and sunlight duration).[3] Tropical and subtropical infections such as yellow fever, dengue, malaria, Lyme disease, Zika virus, chikungunya, trypanosomiasis, Ebola and others, will reach more temperate regions, putting a strain on clinicians and healthcare systems.

As a prime example, tick-borne encephalitis (TBE) historically affects people living in a narrow geographic belt or band traversing central Eurasia, from the North of Spain to China, in a season that goes from March to September. Like all other vector-transmitted infections, however, TBE cases are expanding to higher altitudes, greater latitudes, and during colder months.[3]

Poverty and unsanitary conditions help mosquitos proliferate and disseminate the disease. The destruction of forests also disrupts the ecosystem, altering animal behavior and bringing them closer to humans, as it occurs with monkeys, who may also host yellow fever, enhancing the chances of mosquitos to act as vectors. There are now vaccines available against dengue and yellow fever, the latter with proven efficacy and affordable. The dengue vaccine, however, is still expensive while its efficacy and safety remain controversial.[4]

Natural disasters also bring cholera outbreaks and other diarrheal infections. Rising sea levels and flooded coastal cities, together with failed crops and scarce water, might result in massive migrations, with camps and caravans of climate

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refugees living in unsanitary conditions, waiting near the borders indefinitely or walking for months, and zoonotic diseases might emerge from their close contact with animals while traversing forests or eating carcass meat.[5]

To quote Rome's doctor Galen, "… when the entire year becomes wet or hot, there necessarily occurs a very great plague".[1]

Effects of consanguinity on the types of inborn errors of immunity observed

Approximately 1.1 billion people currently live in countries where consanguineous marriages are customary: in Middle Eastern, North Africa (MENA) and West Asia countries, a geographical area that runs from Pakistan and Afghanistan in the east to Morocco in the west, and including South India. Intrafamilial unions are highly prevalent there and can account for 20%−50% of all families.[6,7] The frequency of consanguinity and rates of first cousin marriage can vary widely within and between populations and communities, depending on ethnicity, religion, culture, and geography. Consanguineous marriages are also practiced among emigrant communities from highly consanguineous countries and regions, such as Pakistan, Turkey, Maghreb and Lebanon, now resident in Europe, North America, and Australia.[8−10]

The most common form of consanguineous families are unions between first cousins, where the spouses share 1/8 of their genes inherited from a common ancestor and their progeny are homozygous (or, more correctly, autozygous) at 1/16 (6.26%) of all loci in the genome. Moreover, in many cases the spouses come from several generations of consanguineous marriages, and thus the grade of consanguinity is even higher, and the level of homozygosity is difficult to predict.[11]

Information on the relationship between this prevalent consanguinity and genetic disorders observed in the population is limited. Sociocultural factors, such as the maintenance of family structure and property, ease of marital arrangements, better relationships with in-laws, and financial advantages relating to dowry, seem to be strong contributory factors in the preference for consanguineous unions. In addition, there is a general belief that marrying within the family reduces the possibilities of hidden uncertainties in health and financial issues.[12,13]

Contrary to general opinion, consanguinity is not confined to Muslim communities. Many other religious groups, including the Lebanese, Jordanian, and Palestinian Christian populations, also practice consanguineous marriage, although to a lesser extent than among co-resident Muslims. In the Hindu population of South India, more than 30% of marriages are consanguineous, with more than 20% between uncles and their nieces.[14−17]

Significant secular changes in consanguinity rates have been reported in recent decades in different countries. In Jordan, Lebanon, and among Palestinians, the frequency of consanguineous marriage has decreased. This could be attributed to a number of factors, including higher levels of female education, declining numbers of marriageable relatives, increased rural to urban mobility, and the improved economic status of families.[18−20] In contrast, a trend to higher consanguinity was observed in Qatar and Yemen, probably based on a belief that the benefits of consanguineous marriages can outweigh the genetic risks, and also because of misconceptions regarding the nature of inherited diseases. However, variability in the composition of the populations sampled across generations make such observations difficult to confirm.[21,22]

Public health concerns centered on the role of genetic diseases as causes of severe morbidity and mortality are likely to increase with the declining prevalence of infectious diseases. On the other hand, social, religious, cultural, political, and economic factors still play important roles in favoring consanguineous marriages among the new generations. This is particularly the case in rural areas and to an extent among highly educated males, but less frequently in tertiary educated females.[23]

An additional phenomenon observed in traditional MENA societies is endogamy (i.e., marriage within the community). This aspect further results in greater intracommunity genetic homogeneity and leads to increased appearance of autosomal recessive diseases. Recessive founder or *de novo* mutations rapidly spread in a local community, causing the birth of affected children regardless of whether the parents consider themselves related or not. Frequently, in inbred societies, even if spouses are not related but are both descendants of founders, they are considered consanguineous. Genetic investigation might be extremely complicated in consanguineous families, due to the probability of multiple mutations in different genes originating from common founders, a phenomenon that has been reported in various ethnic groups.[24,25]

The prevalence of consanguinity markedly declined in Europe, North America, South America, and Japan in the last century, with a more recent reduction among some emigrant populations in Europe. For example, in the Norwegian Pakistani community, the proportion of women consanguineously related to their partner decreased from 45.5% in 1995−1997 to 27.3% in 2002−2005 for those born in Pakistan, and from 48.3% to 18.8% among women of Pakistani origin born in Norway. This trend may be explained by acculturation of the immigrant community, with a gradual transition from their traditional consanguineous marriage preferences to those favored by the dominant group in their adopted country.[26]

There are now approximately 400 single gene inborn errors of immunity (IEIs) underlying phenotypes as diverse as infection, malignancy, allergy, autoimmunity, and autoinflammation.[27] The global incidence of primary IEIs has been estimated to be 1:10,000 live births, although this is considered an underestimation due to limited patient access to diagnostic technologies and the challenges of diagnosing patients with atypical clinical presentations. Although IEIs are rare diseases from a global perspective, they are more prevalent in areas with highly consanguineous populations due to the predominance of autosomal recessive conditions.[28] AR forms, compared to X-linked (XL) or autosomal dominant forms, are clearly the most frequent, with more than 250 known AR IEI genes.

Generally, the high frequency of parental consanguinity and the occurrence of the disease in siblings of unaffected parents are highly suggestive of an AR mode of inheritance. This has resulted in a significant number of these AR IEI being first described in patients from highly consanguineous families. The rapid development of next-generation sequencing (NGS) during the last decade has driven the expeditious increase in the number of recognized disorders, which has led to few consequences. A majority of new inborn errors of immunity are initially described in a single family or a small number of kindreds[29,30].

Publications from a few countries with high rates of inbred marriages have demonstrated a specific distribution of diseases, with a predominance of severe forms such as combined immune deficiencies (CID) and phagocytic disorders, which is in contrast to the predominance of antibody deficiencies in other populations. Furthermore, consanguineous marriages have also been found to affect the types of genetic defects causing these diseases.[31] For example, deficiencies in major histocompatibility complex (MHC) class II and recombinase-activating gene (RAG) 1 or 2, which are transmitted in an AR pattern, are the most common causes of CID in the Middle East, whereas defects in the IL-2 common γ chain, which are XL, are the most common cause of combined immune deficiencies in other parts of world.[32] Another example of differences in the genetic defects in consanguineous populations is chronic granulomatous disease (CGD). X-linked CGD represents approximately two-thirds of CGD patients in western countries, while AR forms of the disease appear to be the most common in regions with higher rates of consanguinity.[33–38] Immunodeficient patients with a history of parental consanguinity have been found to present with more severe PID phenotypes, as documented by the significant numbers of complications, atypical, severe and unusual infections, poor performance status, and a higher mortality rate. This could be due to an overrepresentation of more severe early-onset IEI in these populations.[39]

The scientific value of studying monogenic disorders in consanguineous populations is high, and due to the recent availability of NGS technology, these diseases have been instrumental in the identification of novel and complex phenotypes associated with IEI. The identification of patients with unique clinical and immunologic manifestations within large consanguineous families may enable the recognition of novel disease-causing genes and contribute to the better understanding of immunological pathways and mechanisms.

The burden of IEI on an individual or country level necessitates strategic planning to mitigate their effects. In the MENA countries, the majority of patients have an AR mode of inheritance and come from families known to have the disease. Appropriate genetic counseling for affected families is an essential part of the management. In Saudi Arabia, Turkey, Iran, Israel, and Kuwait, genetic counseling, prenatal and preimplantation genetic diagnosis, and pre-marriage screening to identify carriers are offered to affected families.[40] Such services are costly and require sophisticated diagnostic facilities not available in most of the MENA countries.

Individuals at high risk of having a child with the inherited disease have limited options. They may opt to have no more children, which may compromise the family and break it apart. They also have the option to undergo prenatal diagnosis and, in the case of an affected fetus, termination of pregnancy can be offered, which is unacceptable in some societies due to national laws or traditional or religious issues. Undergoing pre-implantation genetic diagnosis (PGD) to have healthy children is another option. This option requires a collaborative team of immunologists, geneticists and genetic counselors, and the implementation of such interventions and access to genetic services may be limited due to geographic, religious, financial or social factors.[41]

Most patients with IEI are asymptomatic at birth. Early diagnosis and appropriate treatment significantly improve the prognosis and outcome of the majority of these diseases. Severe combined immune deficiencies (SCID) have been recognized as candidates for population-based newborn screening (NBS) using the T cell receptor recombination excision circle assay (TREC) and found to be a cost-effective means to improve survival and reduce the morbidity of diagnosed children who undergo early hematopoietic stem-cell transplantation (HSCT).[42] The high disease incidence seen in regions with a high rate of consanguineous marriages is a critical driving force that would affect the incremental cost-effectiveness ratio. However, health authorities should recognize the importance of such a health problem and provide appropriate financial resources. Israel is the only MENA country performing universal SCID newborn screening. Recently published work showed an estimated incidence of SCID in Israel as high as 4.25:100,000 births, compared to ~1.69-1.72:100,000

reported in countries with low rates of consanguineous marriages.[43] An NBS pilot study is ongoing in Saudi Arabia to identify the real incidence of SCID in the Saudi population.[38,44]

Early genetic diagnosis in patients originating from the same geographical area will help identify patients treatable by HSCT, which is often the only curative treatment, prior to the development of a severe clinical phenotype. Unfortunately, access to life-saving procedures in countries with a high rate of consanguinity and a burden of life-threatening IEI is often very limited.

Founder effects

Homo sapiens has proven to be an incredibly successful, rather invasive, species. Some 60,000 years ago, humans left East Africa in a series of migration waves that eventually covered all the planet. New Zealand and South America were the last corners of the globe to be populated.[45] This out-of-Africa worldwide expansion meant there was a series of small samples of founders from the original population with each successive radiating step or branch; that is, new populations were established by a small number of individuals from the previous, larger population. Each foundation meant a regional decrease in genetic diversity.[46]

This decreased diversity, and the resulting perpetuation of a specific genetic variant from the founders, is what we know as the "founder effect". When most patients with a given IEI in a country or region have an identical variant, that disease may have propagated through that population by a founder effect. This is especially true in geographically confined or endogamic populations, such as the Native American, Amish, Ashkenazi Jews, or the Finnish. In the Czech Republic, the most common pathogenic variant for Nijmegen Breakage Syndrome, a founder homozygous 5bp deletion in *NBN*, can be found in 13% of newborns with microcephaly.[47] Another common explanation for identical variants in non-related patients, is the existence of mutation hotspots in a gene (eg., *CFTR, DOCK8*), or the existence of a pseudogene (eg., *NCF1*), that favor large genomic deletions or DNA polymerase errors.

Founder effects have been described for several IEI. The disclosed patterns of founder mutations are twofold: those that are shared with other inbred populations, and those that are specific to some geographic regions. One of the most illustrative examples for a regional founder effect is the AR MHC class II combined immunodeficiency that has been considered to be a "North-African disease." The original study from Tunisia revealed a founder effect for the highly frequent c.338-25_338del26 mutation (also known as 752delG-25) in the *RFXANK* gene, a 26-bp deletion. The founder event causing this mutation is estimated to have happened approximately 2250 years ago, a period concurrent to the Berber civilization. This is consistent with previous reports showing that the population of North Africa, particularly in Tunisia, Algeria, and Morocco has a common genetic background, and that founder mutations could be shared in some of these countries.[48,49]

Another recurrent mutation is in *VPS45* (c.671 C > A; p.T224A.) which has been identified in 12 Palestinian patients from unrelated families with primary myelofibrosis of infancy; this description was limited to patients originating from Palestine, thus suggesting a possible founder effect for this variant.[50] Furthermore, a recent study reported the recurrence of the same homozygous nonsense mutation (Q289X) in *CARD9* in eight Algerian and four Tunisian patients from seven unrelated families with deep dermatophytosis. This finding was due to a founder effect with the common ancestor living approximately 975 years ago. Additional deleterious founder variants have been reported in consanguineous populations as the underlying cause of a large spectrum of monogenic AR diseases.[51,52]

The clinical implications of the existence of founder effects in a given population include the implementation of preventive approaches through genetic counseling and prenatal diagnosis in affected families. Whole exome sequencing (WES) interpretation should incorporate known regional founder effects as well as variants identified in unique populations.

Regional differences

Deleterious variants are enriched in genomic regions or "runs" of homozygosity found in populations with a high rate of identity-by-descent. Historical bottlenecks and geographical isolation, together with the foundation events, have resulted in relatively recent inbreeding in populations of Latin America.[53] In all the world, there are few true genetic isolates. Latin America has a unique admixture of parental Native American, Iberian and West African populations. Population migration, foundational histories, and sometimes a small population size in a confined space, have resulted in regional differences.

The Central valley of Costa Rica, with one of the highest prevalences of Ataxia-Telangiectasia (AT 3:100,000) is considered to have a high rate of inbreeding,[54] and 4 founder effect variants in the ATM gene account for 76% of patients.[55,56] Similarly, there seems to be a high prevalence of SCID, and at least two founder effects for Hermansky-Pudlak

syndrome in North-West and Central Puerto Rico.[57] In Mexico, there are hundreds of small, closed populations of less than 1000 inhabitants, where tradition and seclusion account for a high rate of inbreeding; founder effects may account for a high prevalence of AT and Griscelli syndromes in Mexican patients.[58]

Argentina has the largest share of European descent in the region: 97.2%, with about 63% of Italian ancestry.[59] Their prevalence of IEI are thus probably more in accord with what has been reported in European and Anglo-Saxon populations. Notably, ever since its inception, the LASID registry has many more patients from Argentina[60–62]; this is, undoubtedly, a testament to their astute clinicians and researchers, but it may also reflect a higher prevalence of IEI in that country.

Even polygenic conditions exhibit regional variation in prevalence. A case in point, Selective IgA deficiency (SIgAd) has been reported to be as frequent as 1:500 in healthy adult blood donors from Caucasian populations[63] in the USA, Europe, Australia and Iran, ranging from 1:300 to 1:3000 (e.g., 1:250 in Lithuanian schoolchildren[64]; 1:651 in adults from Iran[65]). A group in Brazil found the prevalence of SIgAd to be 1:1000,[66] while in China (1:5000), Japan (1:18,500) and India (none) it is far less prevalent.[67–69] SIgAd is seldom seen in Mexico.

Similarly, the share of antibody defects within the pie chart of all defects has been reported at between 25 and 33% (the Middle-East) and 77% (Australia and New Zealand), depending on the country or registry.[70–76] Consanguinity and the proportion of European descent are thought to determine the prevalence.

Vaccines

BCG

Although the *Bacille Calmette-Guérin* (BCG) vaccine, containing live attenuated *Mycobacterium bovis* bacilli, has been proscribed in several countries, it is still mandatory at birth in most of the world,[77] especially in those countries where tuberculosis is endemic (http://www.bcgatlas.org). This is a challenge for the immune systems of newborn children whose immune competence is unknown; infants with T cell or phagocyte inborn errors develop adverse reactions to BCG (local or regional "BCG-itis" or disseminated "BCG-osis").[78] The vaccine-associated disease for SCID is around 40%−50%, while that for chronic granulomatous disease (CGD) is 25%−30%.[79] This is often the first manifestation of disease, as BCG is usually administered before the immune deficient patients have had a chance to encounter other infectious agents. In effect, then, BCG adverse reactions behave as a screening or challenge test in many countries, and IEI should be suspected and ruled out in such affected patients, while formally proscribed in their siblings. As a screening tool, however, it is too dangerous, and immunologists should advocate for a delayed application of the vaccine,[80] starting perhaps at 6 months, when families and clinicians have had a chance to notice or test for anomalies in their patients' immune system.

Polio and other attenuated viral vaccines

The oral Polio vaccine (OPV, Sabin) should not be given to children with combined or antibody deficiencies, as it may cause flaccid paralysis or meningoencephalitis.[81] Not only that, but patients with immune deficiency can show a delayed clearance of the virus and may act as reservoirs[82] allowing for the virus to stay longer, reseed and mutate within a population.

Any immunosuppressed, and some IEI patients with specific monogenic or digenic defects may develop overwhelming infection after varicella-zoster[83,84] (*GATA2, DOCK2, DOCK8, TYK2, IFNGR1, POL3A, POL3C*) or the measles-mumps-rubella (IFNAR1, IFNGR2, IFNAR2 deficiencies) vaccines,[85,86] despite the vaccines' otherwise excellent safety profiles. Any indication of immune incompetence, including failure to thrive or recurrent hospitalization,[83] should alert the provider, who must also always monitor for adverse reactions after vaccination.

The antivaxx movement

Children with severe IEI rely on herd immunity to avoid exposure to infectious agents that are preventable by vaccination.[87] Even the concentration of specific antibodies in a given IVIG batch will depend on the donors' collective immunity. As vaccination rates drop in Europe and the USA, more patients will be at risk of overwhelming infections.

Regional differences in clinical manifestations

Chronic granulomatous disease (CGD)

Most patients (60%−80%) are X-linked (gp91^{phox} deficient) globally, except in the MENA region, where the proportion is inverted (>60% AR disease) due to the high rate of consanguinity.[76] Very few CGD patients in the USA suffer from

mycobacterial infections,[88] but in countries where tuberculosis is endemic and the BCG vaccine is mandatory, susceptibility to mycobacteria is well documented.[79]

Children with CGD are more likely to present with Amebic liver abscess in regions endemic for this protozoan parasite and with poor sanitary conditions. CGD patients inhale Aspergillus spores from organic dust found in compost piles, straw and leaves in garden, forest and farm settings, but also from construction sites.[89] No amount of interferon or antifungal prophylaxis seems to suffice to keep adolescents entirely safe from pulmonary invasive aspergillosis,[90] thus, education on the risks is useful. The current trend toward organic farming may also represent an exposure risk for them.[91]

Recombinant subcutaneous interferon gamma (IFNG) is much more used in America[88] than in Europe to treat CGD.[92] In the US and Mexico, 75%−80% of CGD patients receive IFNG three times a week,[58] while in Europe only around 33% are also treated with it, while most patients seem to do well under antimicrobial prophylaxis alone.[92,93] IFNG was introduced in the 1980s, before the physiopathology of CGD was entirely clear, in the hope of boosting the patients' phagocytes ability to destroy their intracellular prey.[94]

There is one large, multi-centric, well-conducted randomized clinical trial from 1991,[95] that demonstrated a greater than 60% reduction of serious infections in patients treated with IFNG. However, there are some smaller cohorts or anecdotal reports that point to a smaller effect size and to some adverse effects.[93,96–98] More recently, Condino-Neto and colleagues in Sao Paulo[99] reported that IFNG improves the splicing efficiency of *CYBB*, and thus it might be especially (or exclusively) useful in patients with X-linked CGD bearing splice-site variants.

IFNG is, in fact, found increased in the serum of CGD patients, and the prolonged administration of this inflammatory cytokine may, at least theoretically, result in increased propensity to hemophagocytic lymphohistiocytosis (HLH) or systemic autoimmunity, two inflammatory complications that have been repeatedly documented in CGD.[100–104] Interestingly, autoimmune complications in CGD patients seem to be more common in the USA[88,101] and Mexico (around 25%) than in Europe (6%),[92] where they are no more frequent than in the general population (5%).

Hyper-IgM syndrome (HIGM)

In Western cohorts, *CD40LG* is the most prevalent genetic etiology of HIGM, making up nearly 65−70% of all cases and resulting in a more severe form of the disease.[105] Similar to CGD, however, the majority of HIGM patients from MENA countries will have the AR forms of the disease (mainly *AICDA* and *CD40*).[106]

HIGM syndrome has a wide clinical presentation that includes respiratory tract infections, autoimmune phenomena, and a wide range of opportunistic infectious agents. Case series from Brazil and Latin America[107] have found a high incidence of fungal infections, including Aspergillus, Candida, and Paracoccidioides, in addition to *Pneumocystis jirovecii*. Fungal infections affect over 85% of CD40L deficiency cases in South America. Tuberculosis, BCG reactions, *Isospora belli*, and Leishmania infections have also been reported in this patient group.[108]

Gammaglobulin and plasma donors

Nearly all plasma donor centers and gammaglobulin manufacturing facilities are located in the USA and Europe. The concentrations of specific antibodies will depend on the collective immune experience of the donor pool, and those specific antibodies may make a difference on patients with antibody deficiencies under replacement therapy.[109]

Increased awareness has brought an increase of diagnoses of IEI. In Latin America, the prescriptions of immunoglobulins have increased over 130% in the last decade, following outreach and educational programs run by the Latin American Society for Primary Immunodeficiencies (LASID) throughout the continent, and the establishment of Jeffrey Modell diagnostic centers in strategic geographical areas.[110]

Regional centers of plasma donors are desirable in order to increase the diversity of available antibodies in parenteral immunoglobulin preparations. It seems urgent to discuss and approve laws that allow and regulate plasma collection locally, to avoid the dependence on imported products that do not contain the immunologic experience of the population, including antibodies against tropical pathogens. The ethics around the process of donation and shipping of blood, however, must be strictly regulated and supervised, as plasma companies in the past have been known to abuse prison inmates, undernourished Haitians and skid row donors,[111,112] and the blood trade played a considerable role in the HIV and HCV pandemics.[112,113]

Hematopoietic stem-cell transplantation (HSCT) and donor registries

Treatment guidelines and conditioning regimes for HSCT are fairly standardized worldwide.[114] What decides prognosis and survival then, is the availability of resources and each center's learning curve. Two crucial aspects are the donation

culture and donor registries in a given country. When a patient who needs an HSCT cannot find an HLA-compatible donor within his or her family, the probability of finding a matched unrelated donor is higher with donors of their same ethnic background.[115] Moreover, the quest for an unrelated donor might entail graft shipment from abroad, with which waiting times more than double and the total costs skyrocket. Absence of local registries and underdevelopment of accredited stem cell transplantation programs in developing countries can significantly influence and compromise the chances for cure by HSCT.

Transfer factor

In Latin America and Asia, some lesser-known and poorly understood immune modulators are still in use to treat patients with IEI, the most famous of which is Transfer factor (TF). TF, or leukocyte dialysate, is obtained from donor peripheral blood mononuclear cells, mostly lymphocytes, when they are lysed and forced through a semi-permeable membrane that allows only particles between 3.5 and 12 kDa to go through[116]; the resulting dialysate consists of oligopeptides from lymphocytes. Developed in 1955 by Dr. H.S. Lawrence in Rutgers University, TF was thus named because of its observed ability to transfer immunity, or the delayed skin response to tuberculin, from one patient who recovered from tuberculosis to a Tb-*naïve* volunteer.[117]

The pioneers of clinical immunology, including Robert Good, Richard Gatti and Claude Griscelli (and Renato Berron in Mexico) used TF to treat patients from the 1960s to the 1980s,[118–120] and some progress was made at elucidating TF's mechanism of action and molecular nature (see for example, Dr. Charles H Kirkpatrick's work[121–123]). Yet, following the 1980s HIV pandemic, and facing stricter regulations from the FDA, TF was mostly forgotten outside of a few countries such as Cuba, Mexico, Italy and China, where it is still alive and kicking.[124–126]

Today, there even are TF copycats that include bovine colostrum and crocodile transfer factors, which are sold in the streets and as part of get-rich-quick schemes over the internet; TF is promoted by believers: patients, relatives, well-intended clinicians and charlatans alike, and it is supposed to be good for nearly everything immunological: from allergies to cancer, all the way through autoimmunity, infections or IEI.

Other than its proteinaceous or oligopeptidic nature, it is generally accepted that TF is antigen-specific, capable of inducing the release of IFNG and a Th1 response.[123,127,128] In the immunodeficient patient, it is sometimes used to treat chronic intracellular infections, such as laryngeal papillomata or mucocutaneous fungi, always as adjuvant therapy,[129] since its observed effect is modest at best.

TF research fell into oblivion in the US as the result of two events: the onset of the HIV epidemic, with the concern of transmitting the virus through human cell preparations,[127,130,131] and the FDA decision not to allow clinical trials with unidentified molecules. Mass spectrometry, high-performance liquid chromatography and peptide sequencing are some of the techniques that could be applied to learn more about the structure and mechanism of action of TF.

Other cultural or environmental changes

Autosomal recessive variants will continue to be discovered in patients from the MENA and South India, due to the high rate of consanguinity and births in the region. However, the encounters of patients with microorganisms, and the conditions in which they coincide, will determine their clinical presentation around the globe.

Biological diversity is greater around the equator, where the Earth receives more heat. Susceptibility to tropical infectious diseases, including parasites transmitted by vectors, will manifest themselves in patients from these latitudes, or in those returning from travels to the tropics. This, of course, will change gradually, as parasites and other life forms move toward the poles, increasingly more temperate, complicating the epidemiological landscape.[132]

In addition to changes related to global warming, there can be infections that erupt abruptly, as evidenced by the SARS and MERS coronaviruses, HIV, Zika, Chikungunya and Ebola during the last four decades.[1] Viruses and other microorganisms are continuously evolving through spillover from other species,[113] mutating to adapt to their new hosts, subject to their own genetic bottlenecks and founding events.[133] A few examples of recognized threats to patients are given:

- Tick-borne viral encephalitis (TBE), dengue fever, zika virus, entamoeba encephalitis, visceral leishmaniasis, trypanosomiasis, avian flu, chikungunya, may all affect patients with hypogammaglobulinemia, innate immune defects, or T-cell deficiencies.[5]
- Viral hepatitis currently affects over 400 million people worldwide, in a silent pandemic that is expected to peak, bringing a tragic toll of disability and death by cirrhosis, liver failure and cancer. Patients with innate immune, antibody and cellular defects, all have increased susceptibility to viruses and are at risk of acquiring Hep B and/or C viruses.

- Gastrointestinal infections caused by intracellular Gram-negative bacteria, such as Salmonella and Shigella (including dysentery and typhoid fever) are more prevalent in places with poor sanitation and high temperatures during the summer.
- Malaria has been called the ultimate ecological disease.[1] Both the parasite (plasmodium) and the vector (the female Anopheles mosquitoes) thrive in wet, warm settings with stagnant water, such as settings seen with deforestation, floods and poverty in Africa, the tropics or around the Mediterranean basin today, where Malaria causes over one million deaths of children every year, mostly during the fall.
- Another killer of at least one million humans every year, tuberculosis is transmitted by droplets in close contact. Mycobacteria love dense cities, dirt and squalor.[1] Patients with MSMD or CGD might be affected by urbanization, overpopulation and impoverishment in a globalized world.
- Turtle pets are known to carry salmonella. Turtles and other reptiles (lizards, snakes, geckos, dragons) are becoming increasingly popular as choice of pets.[134]
- Foodborne and waterborne parasites, including the cysticercosis-causing *Taenia solium*, or the sclerosing cholangitis-causing *Cryptosporidium parvum*, will infect patients living in, or returning from, countries with unsanitary conditions. Primary sclerosing cholangitis, caused by waterborne protozoa (cryptosporidium and microsporidia), can greatly complicate the prognoses of children with combined immune deficiencies. Contaminated water and dog saliva harbor these parasites.
- Dishes that include raw animals (fish, rodents, frog, snake), undercooked meat or poorly prepared salads, may result in exotic infections such as those caused by *Yersinia pestis*,[135,136] roundworms or hookworms.[137]

Endemic and emerging infectious diseases

Infections with a regional distribution can represent a diagnostic clue to an IEI. This section lists several emerging infections and the immune deficiencies with unique susceptibilities.

Tick-borne viral encephalitis (TBE), Dengue fever, Zika virus, Entamoeba encephalitis, visceral leishmaniasis, trypanosomiasis, avian flu, Chikungunya, may all affect patients with hypogammaglobulinemia, innate immune defects, or T cell deficiencies.[5] Most tick-borne diseases are more severe in the elderly. Although few cases in immune deficient individuals have been reported, they likely represent hosts with altered manifestations.

Hydroa vacciniforme-like lymphoproliferative (HVLL) disease is a curious disorder of childhood endemic to Japan, Peru, Bolivia, Guatemala and a couple of states in Mexico, where it is also known as Ruiz-Maldonado's disease. It involves cutaneous hyper-sensitivity to UV-light (and/or mosquito bites) with disfiguring ulcers and scars, Epstein-Barr virus (EBV) chronic latent infection, and T cell cutaneous lymphoma.[138] While many patients follow an indolent chronic course, some may develop systemic lymphoma with T cell or NK cell monoclonal proliferation. In addition to having a susceptibility to EBV and cancer, with a seemingly demonstrable hematopoietic cell phenotype,[139] HVLL has been reported in a patient with GATA2 haploinsufficiency and hemophagocytic lymphohistiocytosis (HLH).[140]

Similarly, endemic mycosis caused by dimorphic fungi (Histoplasma, Coccidioides, Paracoccidioides, Blastomyces, Sporothrix, Penicillium and Emmonsia spp.), when they cause invasive or disfiguring infections, have been associated with interferon gamma immunity defects, autoantibodies to IFN-γ or CARD9 deficiency.[141]

Patients and their families from regions endemic to certain infections depend on their clinicians' suspicion, diligence and thoroughness to find an explanation for their susceptibility. When all else fails, next generation sequencing for unknown pathogens and WES may help identify monogenic causes and delineate genetic susceptibility to unusual infections.

Developing countries

In the United States, TREC newborn screening programs for SCID are mandated. When an asymptomatic infant with combined immune deficiency is detected, he or she may undergo a targeted exome sequencing and HSCT during the following months, thus achieving a correct genetic diagnosis and curative treatment before his/her first serious infection.

In stark contrast, SCID patients in the developing world are still weeded-out by natural selection. Underdiagnoses, diagnostic delay, prohibitive costs and high lethality are the rule. The cost of the TREC assay can reach up to 2−3 times higher after custom duties are applied on imported reactants and material.

To make matters worse, low-income countries must deal with very low ratios of physicians per 1000 people; side jobs for health practitioners with a public-private overlap; and the "brain drain" of trained scientists and doctors who leave for a better paid job in industrialized countries. A healthcare system with scarce, exhausted or distracted physicians and researchers will underserve patients.

There is an ongoing race for gene discovery. The most influential groups in the field (mostly in Europe and the USA) lead this race, as they were able to position themselves as international referral centers for patient samples from all around the globe. Those same centers with state-of-the-art technology and high-impact novel reports, will get most of the available grants and resources globally. To such giants, the rest of the world send their graduates and samples, in effect saturating the system when we all "go for the blonde". Regional networks with specialized laboratories by country with cooperative collaborations, would surely work best in the long run for all the research centers involved.

The next millennium

Right now, it is not clear who will win the war between humans and bacteria. If superbugs prevail over antibiotics, gain-of-function variants and dysregulation disorders of the immune system that result in an exaggerated inflammatory response against infection, may confer a survival advantage for children in the next century, as they presumably did before the advent of antibiotics.[142]

Loss-of-function variants may also be selected. 700 years ago, the bearers of the CCR5-delta32 deletion survived a smallpox epidemic in Europe,[143] and today their homozygous descendants are elite survivors of the HIV infection[144]; one of the unpredictable outcomes of millennia-long, ongoing experiments of nature, and of the evolution of the immune system. Sexual reproduction, through the random crossover of genetic material from our ancestors, and the imperfect replication of DNA, guarantees that at least some members of our species will survive the next pandemics.

Regarding medical students, residents and fellows in training, programs that include basic and clinical immunology, and those that cover microbiology, molecular biology, genetics, bioinformatics and hematology, are better suited to prepare trainees who will be able to recognize, diagnose and treat patients with IEI, as opposed to curricula with an undue emphasis on allergic diseases.

Eventually, the function of every gene in the human genome will be known, and all or most of the variants will have been categorized. We will better understand digenic and polygenic diseases and unravel the influence of the microbiome and epigenetic mechanisms. Sooner or later the cost of sequencing the entire genome will come down to less than 25 USD, all children will have their genomes sequenced at birth, and researchers by then will have acquired the algorithms and computational power to automatically process, map, filter, annotate and analyze all relevant variants, perhaps in a hand-held device.

Many of our current regional differences, and of our diagnostic efforts will have become irrelevant, obsolete then, but in the meantime, there is still much work to do. After all, we are in the business of fighting off natural selection by protecting our patients, the most vulnerable members of the pack; and for that, we need to keep an eye on their weaknesses and their predators, the trillions of microbes with whom we share the planet.

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