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A framework for improving care of patients with immunodeficiencies and marrow failure disorders

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Fortunately, we live in an area of rapid advances in understanding the causes, consequences and treatment of myeloid biology. At the forefront, advances in genetics and genomics allow us to precisely pinpoint mutational events causing many hereditary immunodeficiencies and marrow failure syndromes. Although advances in treatment lag far behind basic understanding of these diseases, advances and opportunities for advances are emerging rapidly. In this issue of *Current Opinions in Hematology* experts review the molecular basis for diseases reflecting genetic abnormalities in host defenses: leukocyte adhesion deficiency, Barth syndrome, Gaucher's disease, and neutropenia as a feature of a variety of immunodeficiency syndrome. Although these conditions are all quite rare, each is also very informative for understanding “how the body works” and how single mutations can have devastating consequences for our patients.

These reports and others in this issue provide us with pathophysiological principals for understanding human diseases. On the other hand, this is very specialized information. For most of us, and certainly for most individuals, this information is not very relevant; it is relevant only if you need it. For the health of the public, we need to think of this information in a framework that leads to early and proper diagnosis, understanding of treatment options and consequences, and good decision making by patients, parents and medical professionals. How can this be accomplished?

In this issue, Hammarström in the paper “Guidelines for newborn screening for primary immunodeficiencies” points to advances in genetic and molecular diagnosis at the optimal timepoint for recognizing rare and challenging diseases. Screening of newborns with a drop of blood is the most important step for early diagnosis. Skillful obstetricians and neonatologists can often quickly recognize major abnormalities of the newborn, but screening technology very early in life leads to precise and important diagnoses. This is particularly important because in the developed world, blood sampling for a whole population is possible at a critical moment in time. Undoubtedly, with a broader application of exome sequencing and whole genome sequencing, a larger and larger number of genetic disorders leading to neutropenia, immunodeficiency and marrow failure syndromes will be recognized very early in life.

One of the biggest challenges facing the medical profession, however, is knowing how to interpret the rapidly burgeoning information base for medicine. Genetic counseling depends upon understanding the consequences of genetics and molecular findings, such as are described in Robert Sokolic's article on “Neutropenia as a feature of immunodeficiency syndromes”. These syndromes primarily affect adaptive immunity. But neutropenia is also a

feature and understanding its frequency and consequences is very important to the patient. We need continually to refresh this body of information to interpret newborn screening and other genetic testing.

Improving on the advice given through genetic counseling and earlier recognition of genetically based disorders depends upon having longitudinal databases of disease-specific clinical information. For instance, if a child is anemic at birth, can we predict the anemia will improve, worsen or remain the same? For immunodeficiency syndromes and diseases causing neutropenia, this is extremely important for protection of the patient from infections and chronic inflammatory conditions such as those described in Dr. Zimmerman's chapter about leukocyte adhesion deficiency syndromes. Patients and parents want accurate information, and the best source of this information is through the creation of databank or registries describing the natural longitudinal course for patients with various treatments and strategies to prevent illness. Although it takes time, understanding prognosis depends upon gathering this clinical information.

Improving care for patients with immunodeficiencies, neutropenia and the marrow failure disorders also depends on translational research focused on finding new therapies. Ideally, new treatments come from molecular understanding of diseases, but they also occur through chance clinical observations. For rare diseases, such as those described in this issue of *Current Opinions in Hematology* progress can only come through aggregation of patients and cooperation among patients, researchers and clinicians. The time is ripe for simplifying the infrastructure to facilitate molecularly based clinical trials for rare diseases, such as those which have led to advances in understanding Gaucher's disease and several related conditions.

Early genetic testing, early genetic counseling, reliable databases on the natural history of rare disease and research to identify new and effective therapies are cornerstones for improving care for neutropenia immunodeficiency and the marrow failure syndromes. We have made a lot of progress, but we still have a ways to go.