Conquering Blood Diseases –
From Research to Patient Care

Paroxysmal Nocturnal Hemoglobinuria (PNH): An Historical Perspective

Edward J. Benz, Jr.

The history of research into the pathobiology and treatment of PNH is beautifully reviewed by Dr. Charles Parker in the keynote paper of this education session. What is remarkable about studies of this disorder is that insights into the causality and manifestations of PNH drew upon new basic science advances that were reported at the American Society of Hematology (ASH), or discovered and clarified by leading figures in the development of ASH. Many of these contributors were not studying PNH but turned their attention to it because its distinctive features offered end points to test their hypotheses. PNH is an example of the unique contributions that the study of (often rare) hematologic disorders has made to the advance of biomedical research. Appreciation of new biologic phenomena, such as the alternative pathway of complement activation or the role of clonality in proliferative disorders, were shown to be relevant to human diseases by study of rare but distinctive blood disorders like PNH. Given this proof of principle, others become inspired to adapt the same approaches to more common diseases as technological progress permitted.

As described in Dr. Parker's review, extraordinarily insightful research in Europe had established that PNH was a distinct form of intermittent intravascular hemolysis by the mid 1940s; moreover, the key insight that a subpopulation of red cells were hypersensitive to lysis in acid had been made and the classic Ham test developed by the time that ASH was founded in 1958. What was missing was an understanding of the mechanism causing hypersensitivity. The classic complement pathway did not seem to be the key. PNH thus became one reason to predict the existence of an alternative pathway; this prediction, of course, turned out to be true. This linked the study of this disorder to the rapidly improving descriptions of immune mechanisms that highlighted the very first ASH meetings. The rest, as noted by Parker, is history. The mosaicism of PNH cell populations with regard to lytic sensitivity, the evolution of methods to measure complement components on cells, the elucidation of the metabolic networks of the alternative pathway, the elucidation of the importance of anchored membrane proteins in modulating biochemical reactions on the cell surface, the links between the clonality of PNH subpopulations in "classical" PNH and the existence of such clones in bone marrow dyscrasias, and the development of a targeted therapy have highlighted plenary and platform session at ASH on almost a yearly basis ever since.

In summary, PNH is one of a number of uncommon but highly distinctive and dramatic clinical syndromes whose direct study in patients has illuminated both the mechanisms of the particular disease and fundamental mechanisms of human homeostasis having broader implications. It is a vital example of how the strong investigative ethos of ASH has proven, repeatedly, that the study of blood disorders provides the paradigm for using science to advance human health.

See the related ASH 50th Anniversary Review articles under the STEM CELLS AND CYTOKINES section of the publication ASH 50th Anniversary Reviews: A Salute to the American Society of Hematology.