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Multi-author Reviews

Developments in sickle cell anemia research, Part I

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Developments in sickle cell anemia research. Introduction

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Linus Pauling inducted sickle cell anemia (SS) as the first member of the distinguished family of 'molecular diseases', in a ground-breaking article in 1949. Since then, hemoglobinopathies including the sickle syndromes, have continued to help advance our understanding of genetic diseases in general, of red cells in particular, and of the pathophysiology of vascular obstruction.

The series of articles published in this issue, span several topics central to the field. The article by Kaul and Nagel addresses the sickle cell-induced vasoocclusion. It seems clear now, that the original concept of vasoocclusion was naive; I am referring to early models in which rigid SS red cells obstructed passive bystander, the microvessels. In effect the process is much more complex and includes the interaction between adhering deformable SS cells and obstructive rigid SS cells.

The article by Adekile and Huisman deals with a problem that is central to sickle cell anemia: the expression of HbF. Individual patients with any of the sickle syndromes have extremely variable levels of HbF with the added complication that the HbF is unevenly distributed among their red cells. HbF is good for SS patients, the higher the level, the higher the amelioration of the phenotype. Hence, it is very important to determine the genetic basis of this heterogeneity since it might not only allow the prediction of clinical severity but also gives us hints as to how to induce the expression of HbF at higher levels. One of the challenges of the field is to graft hereditary persistence of fetal hemoglobin (HPHF) into sickle cell anemia patients. We know the result of such a manipulation since nature has already done the experiment: SS/HPHF individuals are almost asymptomatic. Adekile and Huisman give us an informed progress report on some of these issues.

The field has been clamoring for an animal model since long, to test the pathophysiological hypothesis and to test anti-sickling drugs. The advances of molecular biology have made this possible by the generation of transgenic mouse models. Fabry reviews the present status of this effort and the advances that can be anticipated with the presently available models. Mice and men are anatomically and functionally different. For starters, they have different red cells, both in size and properties, and they have different kidney medulla. Hence, expecting a perfect animal model for any human disease is not in keeping with the obvious. But we can learn both from their similarities as well as from their differences, as Fabry's contribution illustrates.

Finally, sickle cell anemia exists in the world because, based on epidemiological evidence, the heterozygotes for the β^S gene are partially but significantly protected from dying of *Plasmodium falciparum* malaria. This is one of the most powerful selective factors operating on humans, since even today, malaria is the human disease that produces the largest numbers of deaths in the world. There is considerable in vitro evidence of potential mechanisms by which the β^S gene protects the carrier. The availability of transgenic mouse lines that express the β^S gene enable us, for the first time, to address the mechanisms underlying this case of innate resistance to malaria in an in vivo model. Dr. Shear gives an encouraging progress report of this effort in the present issue.

Further work on this field will be reviewed in the next issue of EXPERIENTIA, in which the molecular mechanism of polymerization of HbS, pharmaco-logical interventions aimed at increasing HbF expression, and the red cell volume regulating transport systems and their impact on SS red cells, will be covered.