PNH and the GPI-Linked Proteins

Edited by Neal S. Young and Joel Moss

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Preface

Paroxysmal Nocturnal Hemoglobinuria and the Glycosylphosphatidylinositol-Linked Proteins reflects the recent fortunate coincidence of breakthroughs in basic science laboratories that impact our understanding of disease and of insights derived from the study of human illness that inspire such experiments.

This book critically reviews the clinical character and underlying biology of paroxysmal nocturnal hemoglobinuria (PNH). Early studies of trypanosomes, a parasitic scourge of humans, led to the discovery of the glycosylphosphatidylinositol (GPI) anchor and eventually to the association of the red cell defect in PNH patients with the mammalian family of GPI-linked proteins. The recognition of a deficiency in a distinctive class of cell-surface proteins and of a single acquired genetic defect in hematopoietic stem cells has allowed definition of the genetic and biochemical nature of this strange disease. After more than a century of observation and study, we now understand how severe red blood cell destruction, life-threatening thrombosis, and aplastic anemia can be combined in a single patient, and the specific lesion responsible for intravascular hemoloysis has been defined. But many provocative questions still remain, ranging from the physiologic roles of GPI-anchored proteins and membrane rafts in the cell to the relationship between a protein defect and profound marrow failure.

The authors of this volume are major investigators in biochemistry, molecular biology, and clinical medicine. As editors, we are especially appreciative of their willingness to prepare original syntheses for this monograph, and we hope that the readers will be educated and stimulated by their contributions.

Neal S. Young
Joel Moss

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A Brief History of PNH

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Paroxysmal nocturnal hemoglobinuria (PNH) was one of the first discrete hematological entities to be described, undoubtedly due to the dramatic content of its primary symptom—hemoglobinuria. The passage of red, dark brown, purple, or black urine is readily noted by the patient and induces a distinct impression on the physician.

The Hippocratean writings contain numerous allusions to ''black urine'' and scholars have debated whether they are describing blood or hemoglobin in the urine or simply concentrated urine, because most of the patients were moribund and most likely poorly hydrated. One word used ($\mu\varepsilon\lambda\alpha\nu\alpha$) means specifically black or very dark, while another ($\pi\alpha\chi\upsilon\sigma$, which has the general meaning ''thick'') is used to describe ''concocted'' urine. The latter is clearly concentrated urine of the dehydrated (a not infrequent condition in Hippocrates' case reports), leaving some doubt of the meaning of the former. However, a nocturnal or morning pattern of dark urine is not described, leading to the conclusion that Hippocrates probably is describing hemoglobinuria from malaria (many of the patients were febrile) or from some other cause other than PNH.

In the Middle Ages, up to about the 17th century, close observation of the urine was a primary diagnostic test of the patient's condition; textbooks detail what should be observed and the presumed causes for the changes seen. (Treatises on distinguishing horse urine from human urine were published because apparently the expertise of the physician was tested by substituting it for the urine of the patient.) Although dark black and red urine are described, the nightly pattern of PNH is not.

The first case report which might be of a patient with PNH was that by Charles Stewart, a Scottish surgeon practicing in Archangel, the northernmost

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