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Identifying Bleeding: Go With the Flow

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Identifying Bleeding: Go with the Flow

In this issue of *Haemophilia* the manuscript from Yaoi *et. al.* describes the use of a new microfluidic platform (t-TAS) to examine bleeding associated with severe anemia[1]. The new tool has advantages over most traditional compartmental and global coagulation assays in that it evaluates platelet thrombus formation under conditions of flow and shear stress. In doing so they demonstrate the importance of red blood cells (RBCs) in hemostasis. Specifically, they posit that RBCs act to physically marginate platelets to the vessel wall and enable platelet activation and thrombus formation under high shear conditions. We have often noted prolonged PFA-100 (a test that also involves flow and very high shear) times in anemic patients but long considered this an artifact or limitation of the test. In this study the authors used t-TAS to measure thrombus formation under high and very high shear conditions and demonstrate that this tool correlated with the clinical findings in a young woman with type I mild von Willebrand disease with menorrhagia. The patient continued to bleed and have an abnormal t-TAS in spite of full correction of von Willebrand factor (vWF) levels but stopped bleeding after packed RBC transfusion. They went on to demonstrate using *ex vivo* manipulated samples that t-TAS was sensitive to both vWF levels and hematocrit.

As we enter the post-genomic era laboratory tools to monitor bleeding phenotype have only become more important. Genetics and molecular biology have given us great insight into bleeding phenomena but approaching unanswered questions will require detailed mechanistic understanding of coagulation and better phenotyping. Better phenotyping will rely on new tools such as t-TAS that allow us to examine the role of heretofor unevaluated but important factors in hemostasis including dynamic measures under physiologic conditions and the role of endothelium.

I recently came across a book, entitled *The Sports Gene*[2]*,* that reports on the role of genetics in athletic performance. In the first chapter the author relays a story about major league baseball's best hitters and Jennifer Finch, the star pitcher for the USA Olympic Softball team. Albert Pujols, Barry Bonds and other all stars were unable to hit her pitches. It turns out that the assumption that outstanding hitters rely on coordination and trigger fast reflexes was wrong. Outstanding hitters recognize patterns of arm movement and baseball rotation very

quickly upon release of a pitch and superior recognition guides their hitting. Further studies identified that superior visual acuity, perception and ability to track moving objects are more important to hitting than reaction time or bat speed. An examination of the Los Angeles Dodgers team reveled that more than half of the Dodgers position players had visual acuity of 20/10 or better (which fewer than 1% of the general population have). If we were to look for genetic or mechanistic biology underlying good hitting based on reaction times or bat speed we would be unlikely to find it. Only by identifying that superior visual acuity defines the phenotype of good hitting could we get to the biology. Similarly, if we define laboratory phenotypes based on components of hemostasis without flow condition we would miss the important role of rbcs.

The complex interplay between genes, non-coding DNA, epigenetics and environment constitute so many variables that systematically evaluating them from unbiased perspective exceeds capacity of subjects in the world and they must be evaluated in relation to phenotypes which are often inaccurate, incomplete or mischaracterized. In Dickens' *A Christmas Carol*, Ebeneezer Scrooge is visited by the ghosts of Christmas past present and future. Modern science is now visited by the legends of hematology past present and future. The legends of hematology past used thorough clinical evaluation to identify specific phenotypes and separate them into disorders that allow us to test interventions and improve care. The legends of hematology present have used powerful genetic and molecular biology tools to identify the underlying defects behind these phenotypes and target these defects to improve care. After the completely penetrant monogeneic and deterministic environmental causes of disease have been determined through state of the art genetic and molecular biology evaluation there will remain many important unanswered questions. The legends of hematology future will need to incorporate mechanistic gene and protein level understanding of biology into complex physiologically driven models, combining this with new tools and understanding of complex phenotypes to improve our understanding of hematologic diseases and improve care for our patients moving forward. Yaoi *et. al.* have reexamined the laboratory phenotype in bleeding patients using an important new tool that incorporates flow and shear enabling us to identify

factors and further characterize bleeding phenotypes previously unrecognized in the clinical laboratory.

1. Yaoi, H, Shida, Y, Ogiwara, K, Hosokawa, K, Shima, M, Nogami, K. Role of red blood cells in the anemia-associated bleeding under high shear conditions. Haemophilia

2. Epstein, D. J. (2013). *The sports gene : what makes the perfect athlete*. Penguin Books.