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Mathematical model of the life cycle of red blood cells may predict risk of anemia

BOSTON, Mass. (November 12, 2010)—A collaboration between a physician-researcher at Massachusetts General Hospital (MGH) and a mathematician from Harvard University has led to development of a mathematical model reflecting how red blood cells change in size and hemoglobin content during their four-month lifespan. In their report published online in *PNAS Early Edition*, John Higgins, MD, MGH Center for Systems Biology and Department of Pathology, and L. Mahadevan, PhD, Harvard School of Engineering and Applied Sciences (SEAS), also describe how their model may be used to provide valuable clinical information.

"This study describes a promising way to predict who is likely to become anemic before they actually do, and it is based on tests routinely performed in hospitals," says Higgins. "More generally, we found that a type of mathematical analysis commonly used in physics can be applied to clinical data and uncover new details of human physiology which can help improve diagnosis."

Mahadevan adds, "We show that it is possible to use minimal models to compress the information available in existing clinical data into a few parameters, which can then serve as a quantitative basis for comparing characteristics across the entire population." He is also a member of the Harvard University Department of Organismic and Evolutionary Biology and the Wyss Institute for Biologically Inspired Engineering.

In healthy adults, around 250 billion oxygen-carrying red blood cells (RBCs) are released from the bone marrow each day, and a similar number are cleared from the bloodstream. While a good deal is known about how these cells initially develop from blood-system stem cells, much less is known about how RBCs mature and are eventually destroyed. Recent studies have revealed that very young RBCs, which are larger and have higher hemoglobin levels than mature cells, experience a rapid loss in size and hemoglobin content during their first few days. As the cells mature, they continue to lose both volume and hemoglobin, but at significantly slower rates.

For the current study, the investigators worked to develop a relatively simple mathematical description of how the volume and hemoglobin content of the average RBC change over time. Starting from the known characteristics of young and mature cells, they developed equations that approximate how the young cells are transformed into mature cells. After building their model with data from healthy individuals, they discovered that data from patients with three types of anemia correspond to different parameter values in the model.

For example, it appears that RBCs from healthy individuals are cleared from the bloodstream before they shrink beyond a specific size. But in patients with mild iron-deficiency anemia or a genetic condition called thalassemia trait, RBCs continue shrinking past the clearance threshold for healthy cells. By looking for an increasing population of small RBCs in blood samples from individuals who had a normal blood test and then went on to develop iron-deficiency anemia 30 to 90 days later, the investigators were able to predict the development of iron-deficiency anemia.

"Looking for the initial shifting of this threshold may allow us to identify a developing anemia significantly earlier than we can now," Higgins says. "Unexplained iron-deficiency anemia in adults is often a sign of a much more serious disorder. One study showed that 11 percent of those with iron-deficiency anemia not caused by obvious bleeding actually had colon cancer. In cases like those, diagnosing anemia 90 days earlier would be comparable to diagnosing the underlying cancer 90 days sooner."

An assistant professor of Systems Biology at Harvard Medical School, Higgins notes that the expertise Mahadevan brought to their collaboration was invaluable. "There are very few mathematically sophisticated scientists who are as knowledgeable about biomedicine as Mahadevan, and his boundless curiosity enables or even compels him to understand any necessary aspects of the biological system. He has repeatedly shown how complex math can lead to simple intuitive models of biological phenomena, and it's these simple models that truly advance our understanding."

Mahadevan, the de Valpine Professor of Applied Mathematics at the Harvard SEAS and a professor of Organismic and Evolutionary Biology, says, "Bringing clinical data, mathematical and computational expertise and scientific culture together to bear on problems connected to the practice of medicine is precisely what is needed to bring medicine towards becoming a finely tuned quantitative subject. John's rare combination of knowledge, talents and enthusiasm are a wonderful example of this approach."

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