

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Systems Biology and Red Cells

David J. Weatherall, M.D.

The remarkable advances in molecular and cell biology over the past half century have revealed layer upon layer of biologic complexity. It has even been suggested that we are reaching a stage at which further progress may be beyond the scope of human imagination, that these branches of science — like physics in its endless search for a unifying theory for the basis of the universe — may be at an impasse.¹ A more optimistic view suggests that if we apply the mathematical approaches of systems biology, many of these

problems may be solvable, although Sydney Brenner has criticized this approach, suggesting that we first try to understand the organization and regulatory biology of individual cells.²

The relevance of systems biology to the interplay between the basic and clinical medical sciences was recently highlighted in a report by Higgins and Mahadevan.³ They used a systems-biology approach to analyze the physiologic and pathologic population dynamics of circulating human red cells. The mechanisms that regulate the number, size, and hemoglobin concentration of normal red cells in circulation — and how these go awry in anemia — are not well understood. It has been established, however, that after their release from the bone marrow red cells undergo a reduction in their volume and total hemoglobin content. To approach this problem, Higgins and Mahadevan used theory from statistical physics together with standard red-cell indexes derived from electronic cell counters to develop a master equation for the maturation and clearance of red cells. Their mathematical model implies that the total number of red cells added to the circulation equals the number removed and suggests that there is a threshold for the mean cellular hemoglobin concentration below which most red cells are cleared from the circulation (Fig. 1).

Quite remarkably, this model appears to clearly distinguish the dynamics of red-cell populations in normal persons from those in persons with anemia of chronic disease, iron deficiency, or α - or β -thalassemia trait. Higgins and Mahadevan suggest that in persons with iron deficiency or thalassemia trait, the persistence of red cells with smaller volumes and lower hemoglobin content, which would not normally be retained, may reflect a compensatory delay in clearance as a result of the less efficient red-cell production characteristic of these anemias. This mechanism does not, however, explain the dif-

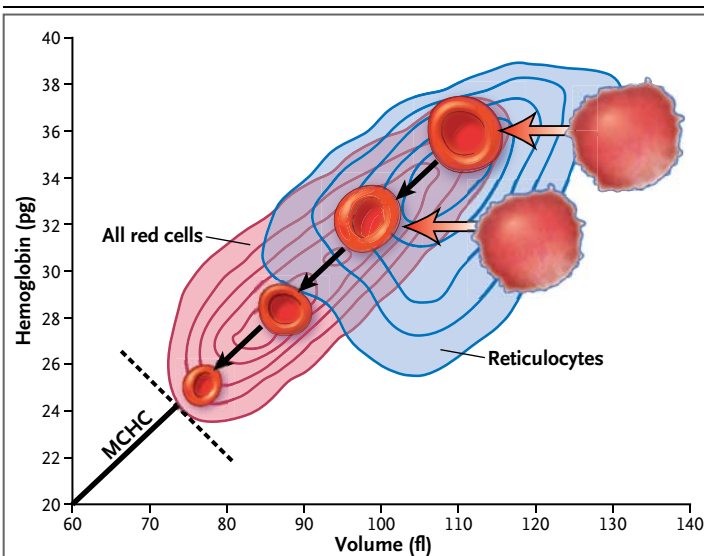


Figure 1. Dynamics of Red-Cell Volume and Hemoglobin Content.

Higgins and Mahadevan recently described in mathematical terms the mechanisms that regulate the volume and hemoglobin content of an average red cell in the peripheral circulation. The reticulocyte distribution is shown in blue and the isoprobability density contours and population of all red cells in red. The diagonal line projecting to the origin represents the average intracellular hemoglobin concentration in the population. A red cell located anywhere on this line will have a mean corpuscular hemoglobin concentration (MCHC) equal to the average concentration. The dotted black line indicates the point at which red cells are removed from the circulation in the physiologic state. Higgins and Mahadevan went on to describe how this threshold is altered in patients with iron deficiency or thalassemia trait, and how related measures may serve to differentiate these two causes of anemia. Adapted from Higgins and Mahadevan.³

ferences in red-cell abnormalities between the two conditions, nor does it explain the differences in abnormalities evident in the various genetic forms of α -thalassemia, an issue that Higgins and Mahadevan do not address.³ Although both the thalassemias and iron-deficiency anemia are characterized by small hypochromic red cells, the red-cell counts in persons with thalassemia trait tend to be normal or raised, whereas in persons with iron deficiency they tend to be reduced. Higgins and Mahadevan found that the degree of variability in the hemoglobin content of red cells is much greater in persons with iron-deficiency anemia than in those with thalassemia trait, which allows differentiation of the two conditions. The mechanisms for inefficient red-cell production in these two conditions are quite different, and there are also differences in terms of red-cell survival and turnover.⁴

Remarkably, the model described by Higgins and Mahadevan appears to be able to predict which patients are likely to become anemic because of iron deficiency in the near future, even though at present their hematologic profile is normal. This observation is also based on evidence of clearance delay.

What are the implications of these findings? They tell us nothing of the intracellular regulatory mechanisms governing the metabolism of red cells, or of the structural changes in hemoglobin or the membrane of red cells as they age during their 120-day sojourn in this unfavorable circulatory environment. However, the model developed by Higgins and Mahadevan certainly raises questions about these mechanisms. As for the potential clinical application of the model, the ability to distinguish between iron-deficiency anemia and thalassemia trait is absolutely cen-

tral to screening programs and to the process of micromapping the traits for different forms of thalassemia in large populations. A survey⁵ of several different discrimination indexes designed for this purpose in screening tests for thalassemia trait has suggested that none of the indexes are entirely satisfactory and certainly do not reach the level of discrimination described in this recent report. However, it remains to be seen whether this new approach will be as robust for use in screening in developing countries, where it is really needed and where the results are complicated by many other issues, including associated infection or other nutritional deficiencies. It is also noteworthy that these studies were carried out in adults. Would the model be equally successful if applied in early childhood, during the normal developmental changes that occur in red-cell indexes?

In short, although the study by Higgins and Mahadevan supports the view that the regulation of dynamic systems will be understood only by means of detailed analysis of the regulatory mechanisms in individual cells, it also shows how knowledge of the dynamics of biologic systems may turn out to have clinical application.

From the Weatherall Institute of Molecular Medicine, University of Oxford, and John Radcliffe Hospital, Headington, Oxford, United Kingdom.

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