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# The Biophysics of Sickle Cell Disease

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Sickle cell disease is the first human disease for which the cause is understood at a molecular level. Thanks to many biophysical studies of structure, thermodynamics, and kinetics, the molecular pathogenesis of sickle cell anemia is better understood than any other protein aggregation disease. Sickle hemoglobin aggregates upon deoxygenation to form fibers that stiffen and distort ("sickle") the red cells. Occlusion of narrow vessels of the tissues by the less deformable cells reduces oxygen delivery, which damages multiple organs and causes episodes so painful that they are called "sickle cell crises". Like amyloid formation, the cause of many neurodegenerative conditions, such as Alzheimer's disease, there is a delay period (lag phase) prior to fiber formation. However, unlike amyloid formation, there is an enormous sensitivity of the kinetics of sickle hemoglobin fiber formation to solution conditions, with the delay time inversely proportional to up to the 40th power of the initial sickle hemoglobin concentration and a primary nucleation rate proportional to up to the 80th power. These extraordinary kinetics, as well as the observation of stochastic fluctuations in the delay for measurements on small volumes due to nucleation of single sickle fibers, can be quantitatively explained with a double nucleation model, a model that has also recently been adopted to explain the aggregation of the Alzheimer's polypeptide. In this seminar I will describe the key kinetics results and the model and show how we are using the results from biophysical studies to understand and treat the disease.

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William Allen Eaton was born and educated in Philadelphia, earning a B.A. degree in Chemistry in 1959, an M.D. degree in 1964, and a Ph.D. degree in Molecular Biology in 1967, all at the University of Pennsylvania. During 1959-60 he studied biophysics at the Free University of Berlin, as the first "Willy Brandt Exchange Student." Eaton's Ph.D. thesis research on single crystal optical spectroscopy of heme proteins was carried out in the Department of Chemistry under the supervision of Robin M. Hochstrasser. He then moved to the National Institutes of Health (NIH) in Bethesda, Maryland, to fulfill his military service obligation as a Medical Officer in the US Public Health Service. Eaton's entire subsequent career has been spent carrying out research in biophysical chemistry at NIH, apart from a semester as a Visiting Professor at Harvard University, Cambridge. Since 1986 he has served as Chief of the Laboratory of Chemical Physics, the principal laboratory at NIH carrying out research in the biophysical sciences.