the energy landscape viewpoint on protein folding [see reference (*1*) in our Perspective]. Smith's observations are in harmony with the energy landscape perspective on protein folding. The robustness of protein native structure to mutation is a consequence of the funneled nature of the energy landscape of a minimally frustrated protein. Kinetic ease of foldability, as we have argued, requires such a funneled landscape in which many of the interactions are consistent with each other. Modifying a few residues cannot dramatically change the final geometry at the bottom of a funnel. Frustrated heteropolymers, which are more common for completely random sequences, have multiple funnels, each leading to a different structure, and which configuration is the actual global minimum depends sensitively on the sequence, unlike natural proteins, which have been selected in evolution. The profound effect of years of selection is apparently to require proteins to obey the principle of minimal frustration.

Smith cites the example of Leghemoglobin, which has no statistically significant sequence similarity to vertebrate hemoglobin but which retains the same basic fold. Goldstein *et al.* have used the principle of minimal frustration to infer effective energy functions for protein structure recognition and prediction. The resulting algorithms do indeed recognize the structural similarity of the two globins (*2*). This shows the consistency and usefulness of the energy landscape analysis in understanding these distant relations.

Smith suggests that the funneled nature of the energy surface is obvious by definition. In fact, it is clearly not a definitional aspect of folding dynamics. Smith cites an experimental observation about proteins as the reason for funnels being "obvious." The question clearly answered by landscape analysis is "Why don't proteins get trapped in deep local minima while random heteropolymers typically would?" There is no longer any need to appeal to mysterious results of evolution.

Despite the naturalness of the qualitative funnel picture, the vast bulk of experimental work on the kinetics of protein folding has focused on the late-stage processes of slow-folding proteins, which are a bit more sequential and rather less parallel in character than the dynamics of the fast-folding stages. Energy landscape analysis explains how the discreteness of these late-stage processes, unlike the final structure itself, is a consequence of the ruggedness of the landscape that is sensed once a great deal of the folding has gone on. The energy landscape theory suggests these late-stage processes are sensitive to mutation and to details of the modeling. Experiment bears this out. In detailed study using nuclear magnetic resonance imaging, Dobson has shown that both hen egg-white lysozyme and human lysozyme, which share a common native structure, have different late-stage intermediates in folding (*3*). The energy landscape analysis suggests that the earlier and more important processes of self-organization are common to these sequences and follow the funneling mechanism restated by Smith. These events can be studied by simple models.

One significant aspect of the energy landscape analysis of protein folding is that it shows how one can reconcile different features of the mechanism of folding with the overall shape of a free energy surface. Equally important, however, is that it allows us to begin the quantitative analysis of folding dynamics. Using the energy landscape perspective to develop the mathematical correspondence between simple models and real proteins is an important step in moving from the qualitative philosophical discussions of protein folding mechanisms, which have been with us for many years, to a quantitative scientific understanding.

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Corrections and Clarifications

In the news article "FDA puts the brakes on xenotransplants" by Rachel Nowak (5 May, p. 630) the description of the response of Columbia Presbyterian Medical Center in New York City to one of its investigators' proposal to test baboon-to-human heart transplants was incorrect. In fact, Columbia convened one panel of outside experts to advise its internal committees on the risks of xenotransplantation, and has since retained two outside experts as consultants to Robert Michler, the principle investigator for the xenotransplant trials. The institution also recommended that a group of experts on emerging infections be convened to examine the risk of viral transmission associated with xenotransplantation (Letters, 21 Apr., p. 349).