A 1986 article by M. Zuker with this title, published in an AMS collection, outlined several major questions in the area — many of which are still relevant today. Stating the folding problem is simple; given an RNA sequence, predict the set of (canonical, nested) base pairs found in the native structure. Yet, despite significant advances over the past 25 years, it remains largely unsolved. A fundamental challenge identified by Zuker was, and still is, the “ill-conditioning” of discrete optimization solution approaches. We revisit some of the questions this raises, and present recent advances in considering multiple (sub)optimal structures, in incorporating auxiliary experimental data into the optimization, and in characterizing sequences for which the optimization does give satisfactory results. (Received September 19, 2011)