Preface

Open any book on biochemistry and you are likely to find statements of the following forms:

"It is well known that hydrogen bonds do not contribute significantly to the stability of proteins."
"It is well known that hydrophobic interactions are the most important driving force for protein folding."
"It is well known that the native structure of a protein resides in the global minimum of the Gibbs energy landscape."
"It is well known that the idea of iceberg formation explains the hydrophobic effect."

Such statements are not only typical in textbooks of biochemistry, biophysics and molecular biology, but also frequently appear in the opening sentences of articles in scientific journals.

Usually, such statements will be followed by a few references which presumably contain the "proof" or at least the supporting "evidence" for the validity of the statements. By providing these references the author can continue to build on the opening sentence without feeling the need for further justification, explanation or clarification of the statements.

After all, if something is "well known," why bother with any details which will be at best superfluous.

Most readers of such articles would accept the validity of such statements, especially when the references given are to articles published by famous and well-recognized authorities in the field. However, if you want to check the validity of the statement and look at the articles referred to, you may find similar statements such as "It is well known ...," "It is well established ..." or "Convincing evidence was given by ..." and more references to earlier literature.

Continuing this process, you will eventually reach the *origin* of the statement, where someone made a *conjecture*, a *hypothesis*, a *plausible* argument or even a *guess* — anything but a *proof* or *convincing evidence* for the validity of the statement.

The purpose of this book is to critically examine the validity of the *original statements* (or hypothesis, conjecture, etc.). All of these statements pertain to the so-called protein folding problem (PFP).

The introductory chapter will briefly present five myths which originated from well-known and well-respected authors. The next five chapters will present in-depth analysis of these five myths and their origins:

(1) From Frank and Evans, "iceberg" idea to "explanation of the hydrophobic effect."
(2) From Schellman's experiments to Fersht's "hydrogen bond inventory argument."
(3) From Kauzmann's conjecture to the "dominance of the hydrophobic effect."
(4) From Levinthal's question to the "solution of Levinthal's paradox."

(5) From Anfinsen's hypothesis to searching for the "folding code," or "predicting" the structure of protein by searching for the global minimum of the Gibbs energy landscape.

Each chapter begins with a short description of a myth, then examines its origin and its evolution, and eventually is debunked.

The last chapter, Chapter 7, is devoted to a few potential candidates for developing into new myths. I am referring, in particular, to two recent "principles" which were introduced into the literature on protein folding. I share with Wedemeyer and Scheraga (2001) the hope that these recent canards will soon vanish from the literature.

All the material discussed in this book has already been published in recent articles in scientific journals. None of these articles were easily accepted for publication. I am well aware of the fact that what I have written has enraged those who propagate these myths. The most surprising finding is that all of these myths continue to thrive and feature even in the most recent textbooks despite the mounting evidence which invalidates them. I will discuss the reasons for such a lingering survival of the unfittest theories in the Epilogue.

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