Key for BioConcept Questions, Chapter 11

1. What are some reasons why knowing the three-dimensional structure of a protein would be valuable?

   Among many reasons: (1) Identifying targets in disease-related proteins for therapeutic agents, (2) Understanding how the various regions of amino-acid structure contribute to the function of the protein, (3) Recognizing similarities between related proteins that are not obvious at the sequence level, (4) Understanding the correlation between amino-acid sequence and three-dimensional structure (leading to eventual prediction of structure from sequence), (5) Studying how proteins interact with each other and with other molecules in order to function biologically.

2. Both secondary and tertiary structures of proteins are three-dimensional structures; what is the difference between the two?

   Secondary structures result from the folding of local areas of the amino-acid chain into three-dimensional arrangements such as α-helices and β-sheets. Tertiary structures are built by the interaction of these secondary structures to yield an overall three-dimensional structure for the whole protein.

3. What are some characteristics of amino acids that help determine how they will participate in the folding of the protein?

   The side chain of each amino acid determines its properties, such as hydrophobicity, charge, length, bulkiness, availability of atoms to form hydrogen bonds, etc.

4. Sickle-cell anemia results from changing a single hydrophilic amino acid (glycine) found on the surface of the folded protein to a hydrophobic amino acid (valine). Discuss how the hydrophobicity of the amino acid could be so important in this disease.

   Hemoglobin is a protein that functions in the cytoplasm of the cell. Like all cytoplasmic proteins, it must be able to dissolve in that watery environment; this means it has to fold so as to put hydrophilic amino acids on the outside, in contact with the solvent. Placing a hydrophobic amino acid on the surface creates a patch where water molecules cannot interact with the protein; in order to minimize the effect of this change, the hydrophobic patches on individual hemoglobin molecules will interact, resulting in large protein aggregates rather than soluble protein.

5. The amino-acid sequence of a protein clearly must determine what folded structures are possible for that protein. What other factors contribute to the structure that is actually chosen? What complications arise in trying to predict a folded structure from an amino-acid sequence?

   The fact that the protein begins folding as it emerges from the ribosome is one factor that determines the folded structure: a β-strand near the beginning of the sequence can't interact with another near the end if one in the middle forms and interacts first. The protein may also contain signals that direct it to the ER, an environment with different characteristics than the cytoplasm, affecting ionic and hydrogen bonds. Even in the cytoplasm, the exact conditions of the environment in which it folds (e.g., pH, salt concentration) are likely not known with certainty, and small variations in temperature can also affect folding. The enormous number of possible configurations of the protein as well as the often-unknown impact of factors such as these makes *de novo* prediction of a folded structure a daunting task.