In this hydrodynamic treatment of proteins, the molecule is assumed to possess some degree of flexibility and solvation. It is represented as an effective hydrodynamic ellipsoid whose axial ratio and volume are determined from measurements of at least two hydrodynamic quantities, all made in the same solvent. [The SC® indicates that this paper has been cited in over 530 publications since 1961.]

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"In the late-1940s and early-1950s, physical chemists were trying to understand the hydrodynamic properties of macromolecules in order to account for their behavior under various conditions. Much of this activity was carried out at Cornell University by Peter Debye, Paul Flory, and Jack Kirkwood. At that time, hydrodynamic data for globular proteins were interpreted in terms of rigid ellipsoids of revolution, in contrast to synthetic polymers for which a flexible chain model was used.

"Leo Mandelkern [now at Florida State University] and Flory had shown that the quantity \( N_s \beta \) was a universal constant for a flexible chain polymer. I wondered whether this constancy might extend to globular proteins. A few calculations showed that it was nearly constant but not quite, and I phoned Mandelkern early on a Sunday morning to initiate a discussion of the problem. Together, we examined the origin of this expression, which we called \( \beta \), and quickly realized that, rather than being a constant, \( \beta \) had to be a function of the axial ratio, \( p \), of an effective hydrodynamic ellipsoid that would have the same hydrodynamic properties as the protein under investigation.

"We abandoned the concept of rigidity for a globular protein by allowing it to be sufficiently flexible to have a variable effective hydrodynamic volume, \( V_e \), and showed how a pair of hydrodynamic quantities enabled \( p \) and \( V_e \) to be determined. Ambiguities in the uniqueness of these calculated quantities were resolved by other hydrodynamic measurements (e.g., of the rotary diffusion coefficient) embodied in a similar function, \( \delta \), whose dependence on \( p \) differs from that of \( \beta \). These ideas were contrary to the conventional wisdom and popular thinking of the time and hence initially engendered an unusual amount of opposition.

"One of the main messages of this paper was that two hydrodynamic quantities are required to obtain \( p \) and \( V_e \) whereas, heretofore, protein chemists often fixed \( V_e \) arbitrarily and placed the burden on \( p \) to account for the hydrodynamic properties of a protein. An illustration of the error in such an arbitrary assumption is provided by a comparison of Tables IV and V in chapter 1 of Protein Structure. Instead, by allowing \( V_e \) to vary (by addition of increasing amounts of urea to denature the protein), it is seen from the data of the cited tables that the protein is flexible enough to swell; thus, the asymmetry (departure of \( p \) from 1) is not as great as had been calculated by fixing \( V_e \) in advance. Despite this demonstration, one still occasionally reads papers in which the hydrodynamic properties of proteins are interpreted by arbitrarily fixing \( V_e \) and then computing \( p \). Unfortunately, in these cases, the problem is compounded further by identifying \( V_e \) with some thermodynamically defined volume. 'On the interpretation of hydrodynamic data for dilute protein solutions' and chapter 1 of Protein Structure provide further insights gained from several years of reflection on the results of this Citation Classic. From the perspective of 30 years later, I retain the same views and interpretation discussed in references 2 and 3. Presumably, the large number of citations implies the acceptance of these views (although not universally) in the interpretation of hydrodynamic data on proteins."