

### Acknowledgements:

Walter Kauzmann in 1942 got me interested in proteins rather than the rockets he and I were working on at that time. This led to my thesis problem at Harvard in 1947 with George Kistiakowsky which was roughly “why are enzymes so large” so the Protein Primer is part of a long-delayed dissertation. It has been built with contributions both experimental and theoretical from almost all of my many associates from Henry Eyring, Louis Hammett, Emil Smith and Henry Frank to the extraordinarily talented students, post-doctoral people, sabbatical visitors and undergraduate dishwashers. The critical papers were those by Mirsky and Anson in the Journal of General Physiology in 1934-35 showing how to completely reverse thermal denaturation but the thermodynamic picture matured only in 1951 when Huggins and coworkers demonstrated the facile rearrangement of disulfide bonds in melted proteins. These set the stage for work at Utah with Emil Smith, Henry Eyring and John Spikes on conformational dynamics and enzyme mechanism. Then Shiro Takashima and Bo Malmstrom got me up and running at Minnesota much as John Schellman did in 1949 at the University of Utah. Bo’s student Andreas Rosenberg came in to set up the proton-exchange program probably our single most profitable undertaking. Rodney Biltonen and I in 1964 organize the many observations made members of our group with which most of the remaining details of protein construction and enzyme function became obvious. However the protein substructures discovered by Kai Linderstrøm-Lang in the first proton-exchange experiments came into clear focus in 1982 with the application of Provencher’s numerical transform method by Roger Gregory. Roger, Carmel Jolicouer, Ezio Battistel and Fennell Evans were the most recent contributors. The proton-exchange work revealed not only the substructures but also the unique importance of packing and free volume in proteins and then in all of biology. Duncan McRee’s graphics program Molecular Image emphasizes temperature and the contributors to the Proton Databank have provided the factors themselves without which modern protein chemistry would have been impossible. The temperature factor, a little-used by-product of x-ray-diffraction work, was another piece of good luck leading with high precision directly to the ubiquitous construction characteristics of enzymes and the nutcracker mechanism to provide cumulative proof for the mechanical mechanism advanced by Eyring, Lumry and Spikes in 1953. It is interesting that even at that time Henry Eyring did not think enzymic catalysis could be explained by small-molecule chemistry and thermal activation of rates, right again Henry. Another noteworthy Henry tour de force in that of Henry Frank

who had water and aqueous solutions correctly explained in 1945 forty years before Walrafen's elegant proof that Roentgen in 1892 was right about the two macrostates of water Those findings supplemented by Benzinger's discovery of the major errors in applications of thermodynamics made the final attack on the remaining puzzles of protein-water interaction possible and Jeffries Wyman's clear thinking about linkage system later extended by Stanley Gill provided the formalism of cooperation in such systems on which the future can be built. It is depressing that so many of the people mentioned in this summary are dead. They have left a brilliant legacy but one not yet known or appreciated.

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