Preface

This is a timely book. It is being published as all the information stored in our DNA is about to be revealed, but demonstrates convincingly why this accumulated nucleic acid-based knowledge can only take us so far. The human genome might enable us to predict the proteins that can potentially be generated, but not where and when or at what level. It cannot tell us the cells in which proteins will be expressed or at which stages of development or differentiation this will happen. Nor can it take into account the enormous diversification of structure that results from alternate splicing, gene insertion, switching by deletions and recombination and other kinds of rearrangements as seen, for instance, in the immune system. Gene structure alone tells us very little about the physiological function of proteins since it ignores the co- and post-translational modifications to which they are subjected, such as their processing by limited proteolysis, their glycosylation, prenylation, ADP-ribosylations etc., and, of course, reversible phosphorylation.

The regulation of cellular processes requires a myriad of commands, positive and negative, to keep under control all reactions that take place and to make sure that no crucial event occurs at an inappropriate time or place. And we know today that the predominant signal that orchestrates these reactions, that turns the switches on and off, relies on protein phosphorylation. This is present to such an extent that at least 30% of all the proteins found in a mammalian cell extract exist in a phosphorylated state, even though one wouldn't know whether all these phosphorylation reactions are physiologically significant.

But even if we had all this knowledge at hand, one wouldn't know how cells react to given signals or, in multicellular organisms, synchronise their behaviour in response to internal or external demands. The modified proteins that are ultimately generated are only the words used by cells to transduce their signals or communicate with one another. For sentences to be constructed or for cross-talks to be initiated, proteins must interact with target, adapter or docking proteins and cells must interact with cells. This requires a plethora of binding motifs (e.g. the src homology SH2 and SH3 domains, or the PH, WW, PDZ domains), some no longer than a few amino acid residues, and further special sequences that determine the localisation of proteins to subcellular elements, direct their translocation in or out of the nucleus, their insertion into the endoplasmic reticulum or the plasma membrane or target them for destruction after internalisation. Cell-cell interaction brings into play an intricate, combinatorial system of cell adhesion molecules, crucial to the

establishment of such highly sophisticated networks of communication one finds, for instance, in the immune system or the far more complex central nervous system where more than a billion cells speak with one another through a million billion synapses, ultimately leading to the generation of thought, memory and consciousness.

In all, then, no matter how distinct proteins might be from one another, they must be viewed as mosaics of structural elements, sorts of necklaces made up of a variety of beads in which each bead carries its own characteristic properties. However, it is the sum of these beads, their choice and particular disposition within the peptide chain that will ultimately determine the overall architecture and function of a protein.

This book, written and edited by those who conceived the notion of proteomics and contributed the most to its development, is the first to offer a comprehensive perspective of the field. It describes authoritatively its origin, fundamentals and background; its methodologies and how the data collected should be analysed, stored, retrieved and applied by the research and industrial scientist as well as the clinician. It eloquently documents how far these new technologies have taken us and where they might lead us in the future.

June 19, 1997

Edmond H. Fischer
Prof. Emeritus of Biochemistry
University of Washington
1992 Nobel Laureate in Medicine