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An overview

The last four decades have witnessed advances on many fronts in the area of amino acids, peptides and proteins. The depth of our understanding and the wealth of detail that has become available has certainly been fascinating. Yet, all this constitutes perhaps only what is a prelude because the scope of virgin territory that remains to be explored is vast and unending.

We should perhaps spare a few words in token appreciation of what has been accomplished. The text books still speak of twenty protein amino acids. And one may remember the classic review on amino acids by Vickery. Now, we recognize the existence of numerous amino acid derivatives as constituents of proteins. Such derivatization results from post-translational modification of proteins whether by enzymatic or non-enzymatic processes. The types of reactions that occur are many—alkylation, glucosylation, phosphorylation, carboxylation, hydroxylation and others. Thereby hangs many a tale concerning the intriguing functional role in the organism of such modification.

The past several years has seen investigators being confronted by an unending stream of what has been termed as the hit parade of peptides. And yet, looking back, when Bricas and Fromageot (1953) reviewed the area of naturally occurring peptides they were constrained to remark that the number then known was not very great and about the paucity of methods for isolating them in the pure state. They had also commented on certain physiologically active naturally occurring peptides being linked to the much larger protein molecules ("mother molecules")· Today we encounter a very large number of peptides which are the result of processing of proteins—such as zymogens, pro-proteins and pre-pro-proteins—by the cell. Certainly, there are others who owe their origin to other mechanisms in the cell. The peptides produced by lower organisms are also countless. We find many of them among the antibiotics.

Of methods for separation and isolation, and analysis there currently is no paucity. Automation has reduced the tedium. The ability to work on a micro scale has been enhanced. It is needless to enumerate specific techniques. Ion exchange and electrophoresis based methods and variations of chromatography such as HPLC and FPLC and affinity methods have been invaluable. Automated sequencing methods and micro manual sequencing methods, with exploitation of solid phase supports, have made structure determination of proteins relatively easy. With rapid sequencing methods for deoxyribonucleic acids becoming available some years ago, the fear had been expressed, that when the sequence of a protein could be so readily made out when the reading frame of a structural gene corresponding to the particular protein is known, regular sequencing methods for proteins would have become redundant. Well, developments in later years certainly bear out what an unwellfounded fear that was! Many hundreds of proteins have been sequenced and the data put to good use—*viz.* in working out evolutionary relationships. It is gratifying to note that large multienzyme

complexes such as the fatty acid synthetase are beginning to be tackled. Occasionally, we do encounter structures amongst small peptides which exhibit types of linkages which are unusual and not found in proteins. Difficulties in structure determination for the chemist with his chemical methods may be so great that only physical methods provide the solution, as in the case of thistrepton of molecular weight less than two thousand whose structure was solved (Hodgkin) by the X-ray method. Crystallographers have now solved with success details of architecture or the three dimensional structure of approximately 250 globular proteins. The classic contributions to this area by Ramachandran, Perutz, Kendrew, Phillips, Kartha and Harker, and Hodgkin—to name just a few—have had major impact in this field. When Biemann and Schemyakin were doing their pioneer studies on the use of mass spectrometry in elucidating peptide structure, few would have been hopeful about successful applications to large structures. Yet, the progress in recent years has been remarkable and one may find that both NMR and variations of mass spectrometry will have increasing roles to play in the future. Any way, the important structural themes in protein architecture seem to have been recognized. On the dynamics of folding and the dynamics of conformational states and transitions increasing attention is being devoted.

One of Anfinsen's contributions is the popular concept that primary structure of a protein determines its tertiary structure. Yet, one may still continue with the query how far is primary structure responsible for tertiary structure. Apart from some cytochromes which have disparate structure, and probably function, but share resemblances in tertiary structure there are instances such as tobacco mosaic virus protein, haemerythrin and apoferritin which are quite dissimilar but exhibit the same tertiary structure—a bundle of four nearly parallel α-helices contributing a pattern not dictated by primary structure but by requirements of helix packing and spatial handedness (chiral connectivity). To account for this, it has been said that structures can be the result of convergence at the three dimensional level after divergence at the primary structure level.

Synthesis, if feasible or desirable, often follows on structure determination. The contribution of solution phase methods to peptide synthesis have been many. In both its manual and automated forms, solid phase synthesis as an innovation has had a very favourable impact. It is gratifying that Merrifield the proponent of solid phase methods has been honoured in 1984 with a Nobel Prize. As Kaiser puts it, "no longer is it necessary for a chemist interested in preparing a peptide 20 or 30 amino acids long to spend a substantial portion of his career in its construction . . . . it is now possible for a graduate student in the course of his thesis studies to prepare as many as five to ten peptides of this size and to characterize their physical and biological properties". The technical advances in synthesis and separation make it now possible to test experimentally hypotheses on structure-function relationships, more thoroughly and with greater ease. Speaking of structure *versus* function, there is great and continuing activity in the study of enzymes, hormones, receptors, toxins and other macromolecules. A whole repertoire of chemical modification methods are brought to bear on the problem. Techniques range from the older unselective reagents, selective ones, affinity labels, photoaffinity labels, radiophotoaffinity labels, enzyme activated irreversible inhibitors (suicide substrates) to a variety of other probes. X-ray methods are exploited too.

On ribosomal and non-ribosomal pathways of protein and peptide synthesis there is great progress and continuing interest. That applies also to areas like tissue proteases and inhibitors, turnover, metabolism and associated metabolic disorders.

Against the above background of world-wide interest and activites in the area of peptides and proteins, the scientific community in India can view with some pride and concern the nature of the Indian effort and contributions. There is certainly much scope for greater participation and involvement in cultivating newer aspects of the field that at present have not many, a few, or no adherents. This particular issue of the *Journal of Biosciences* in no way represents the whole spectrum of activity in India, for obvious reasons. Topics that are covered in the seven papers that are included in the issue touch on binding of water and solutes to myosin, glucoamylase as examined by circular dichroism, the allosteric sites of mung bean aspartate transcarbamylase, bacterial and viral neuraminidases, the location of valinomycin in lipid vesicles, phosphofructokinase of rabbit liver and the nutritional quality of proteins. It is worth remarking that the September issue No. 3 of the journal contained five papers and the October issue No. 4 contained eight papers, out of a total of 12 and 15 papers respectively, dealing with proteins and peptides. It can be hoped that there will be ever increasing number of major contributions to the field in the future.

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