Institute). A. Stracher (State University of New York) discussed the properties of low molecular weight, non-toxic, protease inhibitors such as pepstatin and presented interesting preliminary evidence of their effects in retarding degeneration of dystrophic chick muscle explants and monolayers. The presence of segmental necrosis in Duchenne muscle fibres was stressed by several speakers, and J. Desmedt (University of Brussels) presented physiological evidence for collateral reinnervation of the resulting aneural segments. It might be possible to promote controlled regeneration in dystrophic muscle, with recovery of function after reinnervation.

While there are new diagnostic possibilities, the basic defects in dystrophic muscle remain as elusive as those in cancer cells. Nonetheless, the progress in myasthenia illustrates how advances in basic research can quickly be important in a clinical context. Thus the breadth of the MDA's support, and their personal involvement as exemplified in an address by Jerry Lewis, the National Chairman, offer cause for hope. □

Protein folding experiments: do proteins cheat?

from Barry Robson

THOSE fundamental components of biological machinery, the proteins, are synthesised by the ribosomes of living cells as linear polymers of twenty different kinds of amino acid. Investigators who seek to explain, and even predict, the functional three-dimensional structures of protein molecules on the basis of their amino acid sequences alone are often criticised for neglecting the presence of the ribosome and other biological structures when the protein folds up. Their defence has been that proteins can be unfolded by certain solvents so that a fully unfolded, flexible and random structure is attained, and then refolded without the aid of the ribosome or anything more complex than water, salts, and a healthy temperature and *p*H. Proving experimentally that the amino acid sequence carries all the information for the three-dimensional biological structure is rather like examining a student, however, for in order to prove that the student knows his stuff it is important to ensure that he can think out the problem set to him without taking any written record into the examination room. The experiments of Garel, Nall, and Baldwin (*Proc. natn. Acad. Sci. U.S.A.*, **73**, 1853; 1976) raise the possibility that some protein molecules at least may cheat because they cannot be fully unfolded but retain some elements of their original three-dimensional structure before refolding.

Baldwin's group unfolded the protein ribonuclease A in aqueous solutions of guanidine hydrochloride or urea, and carefully analysed the kinetics of refolding when the guanidine hydrochloride or urea was diluted out. They conclude that the unfolded protein is an equilibrium mixture of two species, one which slowly refolds to the biologically functional, compact state and one which refolds to the same state but 450 times more rapidly. The protein was described as fully unfolded on the basis of difference spectroscopy techniques, which measure the exposure of aromatic amino acid residues to the solvent. Although there is another instance of complete unfolding in terms of solvent exposure, but not in terms of other criteria (Robson and Pain, *Biochem. J.*, **155**, 331–334; 1976) the fraction of rapidly refolding form (about one fifth) is remarkably constant over a variety of conditions. The report of Baldwin's group is thus a cautionary tale: proteins may sometimes cheat because of the invigilance, perhaps unavoidable, of the investigators. Although four-fifths of the unfolded ribonuclease A molecules presumably do not cheat and eventually also reach the correctly folded state, apparently by initial conversion to the rapidly re-folding form (Hagerman and Baldwin, *Biochemistry*, **15**, 1462–1473; 1976), it is possible that there are many proteins with an even more stable rapid refolding form which constitutes a very much larger fraction of the unfolded population. Such proteins would have no option but to cheat, unless some more thorough method or combination of methods of denaturation were used.

Experiments on other apparently completely unfolded proteins have frequently demonstrated complex refolding kinetics, but have not necessarily implied the presence of a stable unfolded and fast refolding form. The relatively unstable intermediates detected in this way are generally believed to represent partly ordered structures initiating a direct and readily traversable route to the folded state, and so guide the folding process. Such guidance or "nucleation" is in fact theoretically necessary in order to account for the rapidity of folding processes which are many orders of magnitude faster than would be predicted from a purely random search of all possible polymer configurations. The question therefore arises as to whether the fast folding species of ribonuclease A is a partly ordered nucleating structure in the usual sense, which just happens to have a high degree of stability.

The authors note, however, that there is an alternative hypothesis based on the proposal of Brandts, Halvorson, and Brennan (*Biochemistry*, **14**, 4953–4963; 1975) that the amino acid residue proline may undergo *cis-trans* interconversion in the unfolded form of a protein. The fast refolding species could therefore represent forms in which all proline residues are in the correct configuration as found in the correctly folded protein. Although purists might argue that such a form would be a "nucleating structure" in the most general sense, the term usually refers to rapidly formed chain structures in which at least several amino acid residues have a fairly specific position in space relative to one another. It would therefore be rather unfair to accuse the protein molecule of cheating if the only structure it retained were the correct configuration of the proline groups.

Even the most detailed test-tube experiments on the configurational statistics of unfolded proteins may not be able to rule out the possibility of small elements of local structure important to the refolding process. Perhaps the real proof that proteins carry all the information for their own folding resides in computer simulations in which the investigator has full control over the initial conformation of the protein molecule. □

NASA Goddard gamma-ray symposium

from F. W. Stecker and C. E. Fichtel

An international symposium on The Structure and Content of the Galaxy and Galactic Gamma Rays was held at NASA Goddard Space Flight Center in Greenbelt, Maryland on June 2–4, 1976.

THE emphasis of the conference was placed on the relationship of γ-ray astrophysics to other fields of galactic astronomy.

D. Thompson and R. Hartman (Goddard Space Flight Center) presented the results from the Second Small Astronomy Satellite, SAS-2. Evidence for pulsed γ radiation from

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