skeptical response from John Maddox[3] of *Nature* who wondered whether the configurational energy E_c was powerful enough to resolve the many inconsistencies of the classical classification.

More recently there has been an altogether different approach to this problem. Magarshak and Malinsky of the Department of Mathematics of the Mount Sinai School of Medicine, New York, have come up with a 'genuinely three dimensional' periodic table. They suggest[4] a three-dimensional stacking of elements based on Hund's rule[5] according to which a spectroscopic term of largest total spin S will be of the lowest energy. And among such terms the ones with largest total angular momentum L are of lowest energy. Since these terms are all well-documented[2,6] it is not difficult to get the three-dimensional table shown in Figure 2. The number of chemical elements in successive periods is given by:

2, 2, 8, 8, 18, 32, 32.

Thus, for instance, in the first period only H and He exist. The second consists of only Li and Be. In the three-dimensional periodic table the third dimension is the periodic number $(n+1)$. All the elements at the same level have same $(n+1)$. A period corresponds to passing from one element to another at the same height from left to right. Group numbers are the accepted classical ones. Projection of this figure along the axis of shell number gives the traditional two-dimensional periodic table. Projection along the axis of period gives a two dimensional realization of Hund's rule. Magarshak and Malinsky conclude: 'We believe that our three dimensional representation is a useful tool for visualizing properties of chemical elements and is in complete agreement with quantum mechanics.'

Interestingly the game started long back by Mendeleev is still enchanting to some. There appears to be still a lot to be probed into.

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G. S. Ranganath is in the Raman Research Institute, Bangalore 560 080, India

On the right *trk*

Mahendra Rao

Nerve growth factor (NGF) is a prototypic member of a family of trophic molecules that include. brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). These low-molecular peptide molecules share structural and topological homology and have both overlapping and distinct effects on the survival of various neuronal subsects.

Two classes of receptors based on binding affinity have been identified — low affinity binding which has a KD in the nanomolar range and a high affinity binding in the picomolar range. The protein which is responsible for the low affinity binding, low affinity NGF receptor (P75LNGFR) has been identified and cloned and shown to bind to all the neurotrophins tested with roughly the same KD. High-affinity binding receptors for the neurotrophins (the TRKs have also been identified. Expression cloning and scatchard analysis have shown partial specificity for neurotrophin binding. For example, TRK-A binds NGF preferentially. But will also bind NT-3 and NT-4/5. Other experiments have shown that TRK expression is both necessary and sufficient to mediate high affinity binding and signal transduction *in vitro*.

These results have left the role of the LNGFR unclear. Several functions have been postulated including aiding in the discrimination between neurotrophins and/or forming high-affinity-receptor complexes (see ref. 1 for review). The first paper discussed demonstrates an important role for the LNGFR and the second paper demonstrates a difference in the specificity of trophin binding to naturally occurring dorsal root ganglion cells and TRK receptors expressed on cell lines by transfection.

Lee *et al.*[2] have disrupted the LNGFR gene and generated transgenic mice which lack detectable LNGFR expression. Analysis of the mice shows that LNGFR plays an important role in neuronal development. Homozygous LNGFR negative mice show a pronounced sensory deficit. Examination of the dorsal root ganglion suggests that this is due to a loss of a subset of sensory neurons. In contrast, sympathetic neurons that are also NGF-dependent appear normal in number and project to appropriate targets. Thus while some trophin functions seem to require LNGFR expression others seem to be independent.

Carroll *et al.*[3] also noted a loss of a specific subset of neurons in the dorsal root ganglion after injecting NGF antibodies *in utero*. The authors were able to demonstrate that the neurons lost were specifically those that expressed the TRK-A receptor (relatively NGF-specific), suggesting that *in vivo* (as *in vitro*) NGF acts selectively on TRK-A expressing neurons. Equally importantly other neurotrophic molecules which are present (and presumably support the non-NGF dependent cells) cannot substitute for NGF in the NGF-dependent cells, suggesting that other neurotrophins cannot bind the TRK-A receptor *in vivo*. Consistent with this result are supporting data from binding studies in primary DRG neurons suggesting a far greater discrimination by TRK receptors, between trophins, than that suggested by the binding data from transfected cells[4]. Further, since the LNGFR is present on both TRK-A expressing and non-expressing cells and since only TRK-A expressing cells are lost after NGF antibody treatment, the LNGFR is not the primary effector of NGF action *in vivo*.

The two papers taken together suggest a possible function for the LNGFR and provide a model for testing this hypothesis. *In vivo* the LNGFR may serve to

enhance the specificity of TRK binding and this could be tested by performing binding studies in the LNGFR-mice. One can perhaps also speculate that NGF effects are independent of LNGFR (consistent with the normal sympathetic phenotye in the LNGFR-mice) but that BDNF which supports a subpopulation of DRG neurons may require LNGFR expression. Examining the TRK subtype expression on the surviving sensory neurons would answer the question. These and other experiments may provide a clearer understanding of the role of *trk* and LNGFR *in vivo*.

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Mahendra Rao is in the Howard Hughes Medical Institute Laboratories, Division of Biology, Caltech, Pasadena, CA 91125, USA

Folding in an unfolded protein

Jayant B. Udgaonkar

For more than 25 years, it has virtually been a dogma to most biochemists, that a protein dissolved in a high concentration of denaturant, for instance, 6 molar guanidine hydrochloride or 8 molar urea, loses its structure so completely that for all purposes it exists in a random coiled conformation. The work leading to this wide-spread belief was elegantly summarized in two classic reviews on protein denaturation[1,2]. The experimental methods used at that time, however, lacked structural resolution. For instance, viscosity and light scattering experiments could show that the radius of the polypeptide chain was independent of sequence for several proteins and dependent only on the number of residues, as expected for a chain with unrestricted conformational freedom, but such measurements could not rule out the possibility that residual structure still existed.

In the last few years, the application of newer experimental methodologies has provided an increasing number of indications (summarized in ref. 3) that the notion of a completely unstructured polypeptide chain needs to be re-examined. Perhaps the most convincing of the recent experiments have been those of David Shortle and his coworkers, whose studies on the effects of certain site-directed mutations on the stability of staphylococcal nuclease could be rationalized only on the basis of the mutations affecting residual structure in the urea-denatured protein. Nevertheless, residual structure in any urea-denatured or guanidine hydrochloride-denatured protein has escaped structural characterization so far. Now Kurt Wüthrich and his coworkers have succeeded in doing just that. In two recent papers[4,5], they report the use of modern two-dimensional NMR techniques to characterize, for the first time, structure in an urea-denatured protein.

The success of two dimensional NMR spectroscopy in the determination of the solution structure of a small protein in solution, relies on the protein possessing a well-defined structure: the chemical shifts of the resonances in the NMR spectrum are then well-dispersed, which permits their sequence-specific assignments. Moreover, the presence of a unique structure usually allows unambiguous use of the NOE (Nuclear Overhauser Effect) data to arrive at a solution structure. The situation for an unfolded protein is very different. The absence of a defined structure leads to poor dispersion of chemical shifts. The presence of multiple conformations in rapid exchange not only means that observed chemical shifts are the averages of chemical shifts for all the conformations (and there will be many for a protein unfolded by high concentrations of denaturant) present, but it also obfuscates interpretation of NOE data. Neri *et al.* have now managed to overcome these difficulties and their work with the 63-residue amino-terminal domain of the phage 434 repressor is the first instance of the determination by NMR of structure in the urea-unfolded form of a protein.

Their success hinged on several factors. The availability of a good bacterial expression system for the 434 repressor made it possible to obtain protein that was selectively labelled with ^{15}N and ^{13}C. Good dispersion in the ^{15}N chemical shifts compensated for poor dispersion in the ^{1}H NMR chemical shifts. The 434 repressor is fully unfolded in 7 molar urea, but under suitable conditions of pH, temperature and urea concentration, the native and fully unfolded forms could be made to coexist in equal amounts. The chemical exchange rate between the two forms was suitable for exchange-relayed NMR experiments: the NMR assignments of the fully unfolded form[4] could be obtained using the assignments for the fully folded native form[6].

Neri *et al.*[4-6] observed a large set of NOE distance constraints for the polypeptide segment 53 to 60, which could all be satisfied by a single well-defined structure obtained using distance geometry calculations and the NOE data. They could not estimate the fraction of the number of protein molecules that possess this segmental structure, but they point out that the calculation of the structure is unaffected by the presence of protein molecules that are completely unstructured. This is important because the chemical shift data indicate that completely unstructured molecules coexist with the partly-structured ones.

The structure that is present in the polypeptide segment 53 to 60 for a significant fraction of the protein molecules is, however, the most definitive evidence so far for the clustering of hydrophobic residues in a polypeptide unfolded by high concentrations of denaturant. This polypeptide segment has four apolar residues, and these residues form a local hydrophobic cluster which is structurally related to a larger hydrophobic core seen in the fully folded protein[5].

There has been considerable recent interest in the proposal[7] that a random hydrophobic collapse is the first step in the folding process, and experimental evidence for such a collapse has been mounting[8]. The detection of a hydro-