Meeting Report:

International Symposium on Nerve Growth Factor (NGF) and Related Substances, held 20–23 April 1986 at Monterey, California, USA.

Nerve growth factor, forty years on

Rarely does a gathering of scientists generate the mixture of excitement and genuine warmth that occurred when 80 representatives of the major neuronal growth factor laboratories from around the world gathered to honour Dr Rita Levi-Montalcini on the occasion of her 77th birthday. We were not to know that this year's Nobel Prize for Medicine or Physiology would acknowledge the contribution that she and Dr Stanley Cohen have made to the study of growth factors, but Dr Cohen's presence certainly added to the 'family' atmosphere. Their great mentor, Dr Viktor Hamburger, was unfortunately unable to attend.

The meeting began with an historical account by Rita of her work leading to the discovery of the effects of NGF in the late 1940s. Whilst all present were aware of Rita's past contributions, many were impressed by her continued output of work into this ever-expanding field, and as the story unfolded it became clear that Rita had more surprises for us. Firstly, that NGF administration has the same dramatic effects on *Xenopus* as have been observed in the avian and mammalian species. Secondly, by demonstrating that mast cell proliferation may be under the influence of NGF, she tempted us to think that the effects of NGF may extend beyond the nervous system. Finally (or rather thirdly, as Rita is not one to retire), that the NGF in the mouse salivary gland may have a function after all, as serum NGF levels were shown to rise and glandular concentrations fall, in proportion to the number of fighting episodes performed between previously isolated males.

The two and a half days that followed were filled with many new and intriguing findings, with only the occasional conflicting data. The first session (Bradshaw, Irvine; Murphy, Harvard; Pantazis, Iowa) summarized the current knowledge of the biosynthesis of the 7S form of NGF including the non-hormonal α- and γ-subunits, and the nature of the processing events required for the production of the mature hormone. Of particular interest has been the isolation of the NGF gene and the production of cDNA probes that has allowed the detection and quantitation of mRNA for NGF. Several presentations using such approaches (Edwards, UCSF; Korsching, Max-Planck/Munich; Bodary, UCSF; Dicou, INSERM) described aspects of NGF synthesis, that sustained the view that sympathetic end organs can elaborate the hormone. Observations from my laboratory (Flinders, South Australia) that Schwann cells are an important source of NGF, emphasized the need for more evidence concerning sites of synthesis, and questioned whether innervated effector cells do produce NGF.

The NGF receptor has proven to be a difficult entity to define but the task has now been at least partially accomplished, in part through the generation of antibodies against the receptor of human melanoma and rat pheochromocytoma (PC12) cells. Several laboratories (Bothwell, University of Washington; Ross, Wistar Institute; Johnson, Washington University; Riopelle, Queens; Heasley, Massachusetts; Sutter, Berlin have used these antibodies and/or [^{125}I]iodoNGF to localize receptors throughout peripheral and CNS. Particularly intriguing was the demonstration that developing skeletal muscle contains a dense population of receptors which rapidly declines with increasing age. Denervation elevates the receptor number more than 25-fold. This increase can also be seen in sectioned sciatic nerve distal to the cut. Since antiserum to S-100 shows a similar distribution, it was concluded that denervation induces production of the receptor by Schwann cells. This finding suggests that some of the previously demonstrated NGF localization to Schwann cells may actually be NGF bound on the membrane via the receptor. Is it possible that NGF secretion by Schwann cells is regulated by auto-receptors, and (as suggested by Johnson), act as anchor points for the NGF, and thus assist in regenerating nerve fibres? The cloning of the NGF receptor/binding protein from melanoma (Chao, Cornell) and PC12 cells (Shooter, Stanford) were major highlights of this session.

PC12 cells have proved to be an important model for the study of the mechanism of action of NGF. Greene (New York University) provided an overview of this model including new aspects of the rapid transcriptional activation of several genes that occurs within a few minutes of NGF treatment. Feinstein (UCSB) provided interesting results that clearly tie NGF action to the production of microtubule-associated proteins (MAP) and the induction of this cytoskeletal structure. A number of phosphorylation reactions are known to follow NGF treatment and these were discussed by Wagner (Harvard), Halegoua (Stonybrook) and Landreth (South Carolina). Guroff (NIH) described evidence for a newly identified protein (NSP-100), whose phosphorylation is blocked and Feramisco (Cold Spring Harbor) discussed the possible role of ras proteins in the differentiation process induced by NGF in this cell line. Microinjection of the oncogenic form of human H-ras protein induced neuron-like morphology and were accompanied by the cessation of cell division.

Whether NGF has a role in the CNS has been debated for many years. However, recent evidence has begun to swing the balance in favour of an endogenous NGF effect on several pathways including the cholinergic magnocellular neurons. Hefti (Miami), Mobley (UCSF), Black (Cornell), Appel (Baylor), Riopelle (Queens), Varon (UCSD) and Cotman (UC, Irvine) demonstrated that these neurons respond to exogenous NGF by elevated choline acetyltransferase activity both *in vitro* and *in vivo*. Like sympathetic neurons, NGF administration can rescue these neurons from death induced by lesions of the fimbria-fornix. Furthermore, both NGF and its mRNA can be detected in the hippocampus. Receptors for NGF have also been localized along these cholinergic pathways, suggesting an association with glial or axonal membranes.

In the final session, Herschman (UCLA) summarized the action of many other growth factors that may act on the nervous system. Unsicker (Philipps University, Marburg) identified new survival factors in chromaffin vesicles and showed that the activity was not associated with any of the well characterized chromogranin molecules. Ishii (Colorado State) showed the ability of insulin-like growth factors to increase specific tubulin mRNAs in an NGF-responsive cell (SY55). While so much has been achieved, so little is understood. For example, it is still not clear how NGF acts, whether internalization is necessary for the biological response (and this is true for NGF acting via nerve terminals), what relationship the other, more recently identified factors have with NGF, or even which cells are responsible for the production of NGF in development and maturity. One suspects 'Rita's factor' will continue to lead us into many more 'unchartered routes' over the next 40 years. Perhaps the organizers can be persuaded to keep us from dangerous waters by making this conference the first of many.

R. A. RUSH
Flinders University of South Australia, Bedford Park, SA 5042, South Australia.

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