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INTRODUCTION

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Neural repair constitutes a theme for discussion rich in tantalizing problems and intriguing new possibilities. At the molecular and cellular levels a host of questions arise about how nerve cells grow to reform their connections after injury. At the other end of the spectrum, it is of obvious importance for both neurobiology and clinical medicine to find out how extensively and effectively repair can be achieved in the brain and how function can be restored. The span of experimental approaches ranges from studies of growth cones in tissue culture to Schwann cell grafts in the mammalian brain, from well-characterized molecules directing neurite extension to dopamine-secreting implants of tissue in basal ganglia.

One clear example of successful neural repair is provided by reinnervation of frog skeletal muscle fibres. Not only do axons start to grow after injury but, following the pathways provided by the distal nerve tube, they reach the muscle end-plates and form effective synapses at just the right sites. Even in this intensively studied system numerous problems remain. What induces the nerve fibres to grow and by what mechanism do they elongate? What are the roles of diffusible molecules in extracellular fluids and of substrate molecules upon which the growth cones find their way? Which cells secrete those diffusible and fixed molecules?

These problems, which even a few years ago seemed quite intractable, can now be approached in tissue culture and in animals by new molecular techniques involving monoclonal antibodies and gene cloning. Until recently, nerve growth factor (NGF) provided the sole example of a well-characterized molecule that had a demonstrable role for growth and survival and that had a specific antibody to block its function. What could not be assessed till newer techniques became available was how synthesis of NGF was initiated and regulated by neurones, Schwann cells and target tissues, how NGF reacted with specific membrane receptors, what types of receptors existed and where they were situated, and how NGF became internalized and was transported from terminals to soma. As the papers in this volume show, remarkable progress has been made in our understanding of NGF in relation to repair as well as growth. In addition, other as yet unidentified, soluble molecules can serve to direct motor nerves towards their targets situated many millimetres or centimetres away from growing nerve tips.

Non-diffusible molecules fixed to the basal lamina are also known to provide cues for neuronal repair. Key questions concern the mode of action of these fixed molecules, their identity and the cells that secrete them (Schwann cells, glial cells,

muscle fibres, motor neurones?). Laminin, fibronectin and N-CAM are molecules of known structure that can induce sprouting, branching or cessation of growth by damaged neurones. At regenerating neuromuscular synapses in the frog, other molecules present in end-plate basal lamina, such as 'agrin', cause acetylcholine receptors to aggregate, motor nerve terminals to stop growing and presynaptic release sites to form. What still seems elusive is a quantitative measure of the relative importance of the soluble and fixed molecules in determining growth rates, patterns of growth and target recognition.

Another important, unresolved question concerns the differences between neurone to Schwann cell and neurone to CNS glial cell interactions. Why is it that in vertebrates Schwann cells provide such excellent conduits for extended growth and CNS glial cells do not (at least in the animal)? Tissue culture, by allowing one to control the environment and alter one variable at a time, has proved invaluable for approaching these questions. Neurones, glial cells and pairs of cells need no longer be black boxes. At a higher level of organization, mammalian slice preparations maintained in tissue culture offer hope for studying assemblies of cells and their reconnection in two dimensions: slices of CNS tissue closely apposed in culture send out processes that grow towards specific targets.

At the same time it is evident that there exist entirely different, more complex aspects of neural repair, requiring experiments made on whole animals, vertebrate and invertebrate, for their solution. What changes do nerves within the CNS, in their natural environment undergo after axotomy with regard to protein synthesis, growth patterns, receptor distribution and synapse formation? Once one knows that CNS neurones in mammals can indeed grow over many centimetres if provided with Schwann cell conduits, an important next step is to know whether they can form synapses with the 'correct' targets. Related problems that can be studied only in animals concern compensatory mechanisms, such as the ability of undamaged neurones to sprout and take over lost functions. And within the animal, non-neuronal cells such as macrophages, microglia or glial cells remove debris and form scars with important consequences for the outcome of regeneration.

Implicit in all studies of neuronal repair is the problem of how realistic it is to imagine that entire circuits could be re-established during regeneration. Amazingly accurate CNS regeneration does occur in some animals (such as leeches, cockroaches and lower vertebrates) – but in mammals? Can one imagine the spinal cord or the frontal lobe rewiring itself after injury? Indeed if widespread regeneration could be promoted in the mammalian CNS an entirely new spectrum of problems would arise. Suppose fibres of the nociceptive system regenerated first and gave rise to intractable pain? At present such speculation seems far removed from reality or practical application; however, much the same would have been said about the advances described in this series just a few years ago. For example, say in 1967, surely no one would have guessed that embryonic neurones or adrenal medullary cells grafted into adult brain could replace a deficit in CNS transmitter, let alone that they could drastically alleviate symptoms resembling those of Parkinson's disease.

It is the combination of extremely varied techniques and fundamental problems that makes neural repair so fascinating a field for study. In addition, the investigators following regeneration are always looking over their shoulders to compare what they observe with advances in a closely related field – development. At each stage one wonders to what extent nerve cells are repeating the same steps to grow back and reform connections as they did during embryogenesis. Differences and similarities are obvious: after you have gone along a pathway once it may be easier to find your final destination. However, competition, timing and cell death which play such a large part in development are not evident in regeneration.

The hope that eventually, albeit in the indefinite future, one may be able to help patients seems far more realistic now that Schwann cell grafts have been shown to allow long outgrowths and new cells can be used to replace dead ones. Unlike many other fields of biology where major advances are being made, studies on neural repair have a certain old-fashioned charm. First, well-tried techniques do not become obsolete. (Nissl and Golgi stains as well as conventional extracellular and intracellular recordings are still useful even though wonderful new, complementary techniques are available.) A second delightful feature for those of us who work in the field is the absence of secrecy or bitter competition. When it comes to problems of such importance, interest and challenge there is plenty for everyone to do.