vitro[11] and subsets of sensory neurons[12].

Comparison of the phenotypes of the *trk*B[1] and BDNF[2] null mutants provides an indication, albeit indirect, of the relative importance of BDNF and NT-4 in promoting the survival of different neurons *in vivo*. Analysis of the sensory ganglia of postnatal BDNF mutant mice[2] reveals marked loss of neurons in those ganglia that have been shown *in vitro* to contain a large proportion of BDNF-dependent neurons. Similar numbers of sensory neurons are lost in the dorsal root ganglia of *trk*B and BDNF null mutants (30%) but more neurons are lost in trigeminal ganglia of *trk*B (60%) than BDNF mice (44%). The most striking difference is that lack of TrkB receptors causes marked reduction in motor neuron number (70% in the facial nucleus and 35% in the lumbar cord), whereas mice without BDNF are normal in that respect. These findings suggest that, *in vivo*, BDNF is important for the survival of certain sensory neurons but not motor neurons, and raise the possibility that NT-4 promotes motor neuron survival. The relative roles of BDNF and NT-4 would be clarified by studying the phenotype of mutant mice that lack NT-4. Moreover, analysis of the phenotype of intercrosses between BDNF and NT-4 null mutants should reveal if TrkB has functions *in vivo* that are additional to the combined actions of its two preferred ligands.

An intriguing finding in postnatal BDNF mutants is that most, if not all, of the peripheral axons of the remaining vestibular neurons terminate in connective tissue short of their target epithelia[2], raising the possibility that BDNF may be involved in axonal guidance. But because the peripheral projection of the neurons was examined postnatally it is not known whether they had failed to reach their targets or whether they had done so and subsequently retracted. This matter of the developmental stage at which observations are made highlights a general need for caution in interpreting the results of these gene-targeting experiments. Because mutations in the neurotrophin and *trk* genes may have developmental consequences very early on, the reduced size of neuronal populations in mutant mice could result not just from the failure of neurons to survive but from aberrations in the proliferation and differentiation of neuronal progenitor cells. This is especially germane given that, *in vitro*, NT-3 can promote proliferation of neural crest cells[13] and BDNF can commit such cells to the sensory neuron lineage[14].

Finally, the *trk*C null mutants. These mice were generated by deleting sequences encoding the kinase domain, leaving non-catalytic isoforms unaffected[4], and most died within three weeks of birth. Notably, though, they displayed abnormal motor behaviour suggestive of defective proprioception (sensory information about limb movement and position). Consistent with that observation, the mice have 20% fewer neurons in dorsal root ganglia and selectively lack group Ia afferents, which innervate muscle spindles. These results are in accord with the demonstration that NT-3 promotes the survival of proprioceptive neurons *in vitro*[15]. Whether *trk*C mutant mice have deficiencies in any of the other subsets of sensory neurons that respond to NT-3 *in vitro* remains to be seen.

Intriguingly, although *trk*B and *trk*C messenger RNA transcripts are widely expressed in the CNS, initial studies have not revealed any gross defects in the CNS of either *trk*B[1] or *trk*C[4] mutants. Although abnormalities may yet be identified, the fact that expression of these two genes overlaps in many regions means that they could be involved in functionally redundant pathways. Intercrosses between individual *trk*B and *trk*C mutants should help here. Another issue that will have to be addressed is the role of the non-catalytic TrkA and TrkB isoforms, because in these experiments their coding sequences were unaltered[1,4]. Mice with disrupted extracellular sequences in *trk*B and *trk*C genes might be informative in this respect.

What next? There is a wealth of detailed anatomical data yet to be obtained from the mutant mice and from intercrosses between them. Moreover, neurons that lack specific Trk receptor tyrosine kinases can now be obtained for study *in vitro*. The contradictory results obtained from investigation of p75 in physiologically irrelevant cell lines illustrate the importance of looking at the function of neurotrophin receptors in the appropriate cellular and developmental context. Thus, analysis of neurons isolated from embryos homozygous for mutations in *trk* genes should improve our understanding of the cell biology of Trk receptors, as illustrated by equivalent studies of neurons from p75 null mutant mice[9]. □

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DAEDALUS

Fair copy

COMPUTERS are still very bad at interpreting handwriting. The 'digital personal assistants' sold for this purpose are little more than expensive jokes. Daedalus points out that handwriting is very much the expression of a personal neural code. Those who learn to write with their feet, or with a pen held in their teeth, continue to produce the same characteristic script. So he plans to intercept the neural handwriting code one step nearer its source. He is devising a machine to read, not the writing itself, but the movements that generate it. He points out that our fingers are operated by tendons connected to muscles in the lower arm. A set of sensors attached to the wrist could read the movements of these tendons. They would be closer to the origin of the handwriting; they would also be dealing with a set of purely scalar values rather than a complex two-dimensional pattern.

DREADCO's technicians are exploring several approaches to this scheme. Their simplest idea is a bracelet carrying a set of piezoelectric movement sensors, each responding to the change of tension in a single tendon as it is operated. Another idea is to implant a tiny magnetic speck in each tendon, and follow their movements by a set of pick-up coils on the bracelet. Less invasively, a magnet on the bracelet could induce a tiny potential across each tendon as it moved; skin-voltage sensors could then read its velocity. This differential signal might be more informative than reading the displacement directly. In each case the outputs from the bracelet sensors would be led by a fine wire to a small neural-net learning computer in the wearer's pocket. It would accumulate examples of his tendon movements until it had learnt his internal handwriting code.

The wearer of DREADCO's 'Wristwriter' will enjoy a new scriptive freedom. He need not look at what he is writing, or keep within the confines of a tiny sensing pad, or avoid overwriting his previous comments. He can scribble in bad light or darkness on any scale and on any surface. For confidential notes, he can use an empty pen or even a wooden stick, leaving no trace except the private record in his Wristwriter. Even if he cannot read his own handwriting, it will still be the outcome of a consistent code of tendon movements. The Wristwriter will read it for him.

The Wristwriter will even be able to interpret other manual activities. It will memorize knitting patterns, and convert spontaneous flute tooting and piano playing into musical notation. Wherever fingers are at work, it will be there to record what they do. David Jones