dent. Uniquely, GDNF seems to prevent both loss of neurons and atrophy of the cell body, though taken alone the clinical relevance of these striking results is debatable. Other studies indicate that the previously reported rescue effects of CNTF (ref. 12) or BDNF (ref. 13) in this rodent model are quite transient[14,15]. Moreover, as a further caution against overinterpretation of animal data, in the *pmn* (progressive motor neuronopathy) mouse mutant, in which CNTF treatment prevents degeneration of motor neurons and thus extends the lifespan of affected animals[16], GDNF rescues motor neurons but has no effect on the premature death of the mice (A. C. Kato and P. Aebischer, personal communication).

Given its initial billing as a highly specific survival and differentiation factor for dopamine neurons, the results of testing GDNF in animal models of Parkinson's disease have been keenly awaited. Tomac *et al.*[6] and Beck *et al.*[7] provide substantial evidence that GDNF does indeed protect or restore function of dopamine neurons compromised by axotomy or the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Although the clinical relevance of their model is questionable, Beck *et al.*[7] clearly show that repeated intranigral injections of GDNF largely attenuate the 40 per cent, or more, loss of dopamine neurons resulting from transection of their axons within the median forebrain bundle. Although this demonstrates the responsiveness of mature dopamine neurons to GDNF, such rescue of axotomized cell bodies does not restore behavioural deficits and so provides only indirect evidence of any clinical usefulness.

However, in a more relevant test of the potential of GDNF to protect or restore dopaminergic function, Tomac *et al.*[6] provide encouraging data from a mouse model of Parkinson's disease produced by the dopaminergic neurotoxin MPTP (which is known to produce parkinsonian symptoms in humans). In one experiment, the authors show that intrastriatal injection of GDNF before administration of MPTP attenuated toxin-induced changes in levels of dopamine and its metabolites, preserved striatal levels of the important enzyme tyrosine hydroxylase, and improved scores in tests of motor function. Furthermore — and this is arguably the most exciting finding — treatment of mice with GDNF days *after* MPTP treatment produced a substantial regeneration of tyrosine-hydroxylase-immunopositive fibres within the striatum, partially restored dopamine levels and improved motor performance.

In all, these effects of GDNF on dopamine neurons are encouraging. But it should be noted that both groups[6,7] resorted to direct intraparenchymal injection of GDNF — this procedure has never been carried out on human subjects, and we don't know about the possible anatomical or behavioural side effects, or how prolonged the restorative effects of GDNF might be.

As the aetiologies of Parkinson's disease and sporadic ALS are unknown, devising ways to arrest these diseases rely largely on broad concepts of how best to interfere with neuronal atrophy and loss. Oxidative stress, excessive Ca^{2+} and glutamate toxicity are high on the list of suspects, but the basic biochemical nature of these processes has made it difficult to prove their guilt or to abolish their deleterious actions on neurons. The striking effects of neurotrophic factors in cell culture and the long list of accomplishments of NGF (and now a variety of other factors) in animal studies makes these molecules attractive candidates as therapeutic agents. But animal models can be poor predictors of adverse reactions in patients. This is highlighted by the confounding side effects of hyperalgesia and weight loss found in clinical trials of NGF (ref. 17) and CNTF (J. M. Cedarbaum, unpublished results), respectively, despite the strong rationale behind these trials and these factors' efficacy in animal studies. Such side effects may, however, be overcome by using combinations of growth factors that have synergetic effects at dose levels that show no side effects[18]. Clinical studies with CNTF, BDNF and insulin-like growth factor-1 (IGF-1) in ALS patients are in progress.

The new reports on GDNF biology highlight how quickly the discovery of ligands is followed by assessment of their therapeutic potential. But further animal studies, and more detail on the distribution of GDNF-binding sites and its general pharmacology, pharmacokinetics, stability and toxicology, are necessary before we can see just how promising that potential is. □

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DAEDALUS

Recycled teeth

LAST week Daedalus was musing on the atomic bomb, in which a hollow shell of high explosive is detonated to compress a central charge of plutonium. He wanted to use the technique on samples or assemblies of animal teeth. Under the sudden massive pressure they should flow plastically, and pressure-weld together into an artificial ivory. He is now applying the idea to human teeth.

Restorative dentistry is bedevilled by the lack of any good substitute for tooth material. Gold is expensive, amalgam slowly erodes, porcelain is hard to shape, and none of them bonds firmly to the tooth beneath. But implosive forming, says Daedalus, would permit human tooth substance itself to be formed into crowns and inserts. The dentist would take the usual wax or elastomer impression, but instead of casting a crown from it, its shape would be scanned into a computer. A program adapted from those of bomb physics would then calculate what pattern of explosive charges would deform what initial sample of dentine into that exact shape. The program could even do the calculation for a composite sample, such as a chunk of dentine in contact with a sliver of tooth enamel. The explosion would pressure-weld the two into a single insert of the desired shape, faced with a hard enamel biting surface.

The ideal material for such an insert would, of course, be tooth substance from the patient himself. This would be immunologically compatible with its new site. It should be welcomed back into the body, and should bind firmly into place by slow protein infiltration. But where to get a sample of the patient's tooth substance, without pulling out another of his teeth? Daedalus recalls the 'milk teeth' we all shed as infants, from the age of about six. These teeth should not be discarded or sold to the tooth fairy, but carefully preserved in liquid nitrogen. They would then be available as raw material for subsequent dental repairs to their original owner.

We grow and shed only 20 milk teeth; they are quite small, and have no root (it is resorbed in the shedding process). This modest reserve of material should still provide a lifetime's supply of crowns and inserts, and could even give a whole replacement tooth as well. To fit in the jaw, such a tooth would need a properly shaped root. It would have to be pressure-welded from several milk teeth, and then forced into its place in the mouth. It should soon bind fast to the compatible tissue all around it, and would then be as good as new. Indeed, it would be even better — having no nerve, it could never ache. David Jones