follow-up, the greatest increase of NfL was in converters, with less evident changes in participants who were already symptomatic. Thus, in genetic frontotemporal dementia, serum concentration of NfL might start to increase 2 years before the appearance of symptoms. These findings are similar to those of a MRI study[4] done on a similar cohort, wherein extensive involvement of white matter and a decrease of grey matter volumes in prefrontal, temporal, cingulate, and insular cortices were seen 2 years before clinical onset. Similar to frontotemporal dementia, in presymptomatic amyotrophic lateral sclerosis mutation carriers, elevated concentrations of serum NfL have been found about 1 year before clinical onset.[5] The relatively short presymptomatic phase of the frontotemporal lobar degeneration spectrum is substantially different from that of familial forms of Alzheimer's disease, wherein presymptomatic carriers of mutations in presenilin-1 and amyloid precursor protein genes show high serum NfL concentrations up to 10 years before the estimated onset of disease.[6] Thus, it seems that the window for early detection of the risk of conversion from the asymptomatic phase to clinical phase of frontotemporal dementia might be particularly short and should be closely monitored. Notably, research interest in the presymptomatic phase has extended to other neurological diseases, such as multiple sclerosis, where serum concentrations of NfL increase as early as 6 years before clinical onset.[7]

These research efforts will hopefully lead to the use of serum NfL as a biomarker to monitor asymptomatic individuals who are either carrying causal mutations of different neurodegenerative diseases or have a strong familiar history for neurological disorders, thus giving them the chance to undergo timely and effective disease-modifying treatments.

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Is a four-limb exoskeleton a step in the wrong direction?

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Before the Second World War, life expectancy for people with spinal cord injury was low, with most people dying within 3 years of injury. The arrival of antibiotics, improved bladder care, and the introduction of new treatments meant that life expectancy greatly increased, and with this increase came greater interest in rehabilitation.[1] Walking was central to this rehabilitation project, with a belief that full independence and productivity can only come through ambulation. A life in a wheelchair was seen as in some way lacking. This view is perhaps best represented by neurosurgeon and founder of modern spinal cord injury rehabilitation Professsor Donald Munro's lengthy diatribe to the Paralyzed Veterans of America,[2] in which he criticised the adoption of a wheel as the symbol of their organisation. Munro stated that, were he paralysed, he would be "ashamed to be photographed in a wheelchair". "Why be represented by an admission of failure?" he argued; "why not have the courage to live greatly and make the symbol what it ought to be—calliper braces or crossed crutches inside a laurel wreath?"

From the 1950s onwards, the promotion of crutch-walking or orthosis-assisted walking has remained the goal of spinal cord injury rehabilitation. In a meta-analysis of orthosis for people with spinal cord injury, Karimi and Esrafilian[3] found little evidence to suggest that there was any improvement in function and that the performance in mechanical and power-assisted orthosis was low. Despite this finding, bioengineers and rehabilitation engineers continue to search for a new solution. Walking, as Mike Oliver[4] has pointed out, is more than a means of

getting around, and terms such as "confined to a wheelchair" or "wheelchair bound" are still in common usage.

In *The Lancet Neurology*, Alim Benabid and colleagues[5] discuss the clinical application of a brain–computer interface system developed for patients with tetraplegia with cervical spinal cord injuries, which enabled bilateral control of the arms and legs of an exoskeleton or a computer avatar, for a 24-month period. An originality of this study is showing the control of four limbs, whereas in most previous studies only one limb was controlled. However, autonomous walking with equilibrium is not so far possible. Although this study presents a welcome and exciting advance, we must remember that proof of concept is a long way from usable clinical possibility. A danger of hype always exists in this field. Even if ever workable, cost constraints mean that high-tech options are never going to be available to most people in the world with spinal cord injury. One analysis[6] suggests that only 15% of the world's disabled population have access to the wheelchairs or other assistive technologies that they need.

People with tetraplegia do already have usable solutions, in the form of lightweight wheelchairs with new generation batteries, and controls that can enable users to drive themselves by blow and sip, by micromovements of one hand, and by other means. Although this study suggests the possibility of replacing a joystick by conscious control, why this is a major practical improvement is not obvious. Highly effective control systems for hoists, beds, living areas, cars, and most other areas of daily life are available, benefiting many people with spinal cord injury. Often, making environments accessible or providing appropriate assistive technology is more effective than trying to fix individuals with injury, particularly in low-income settings.[6] However, our dominant medical mindset seems always to have wanted to make the paralysed walk.

Benabid and colleagues' study does not make space for user views, which is disappointing, although apparently the research participant found his added control to be rewarding. Developments in rehabilitation—whether neurosurgical, therapeutic, or technological—are more likely to be taken up if the views of the potential beneficiaries are considered at the outset. Although a newly paralysed patient does indeed dream of walking again, a person who has adapted to their situation might have other priorities—eg, bladder or bowel management, pain control, or avoidance of pressure sores. Indeed, people with spinal cord injury generally enjoy a good quality of life,[7] regardless of the level and degree of lesion.[8] Understanding the life goals of this patient group would be an important step towards collaborating on a genuinely useful medical or technological advance. Ending the focus on moving limbs might assist people who have had trauma in adapting to their situation.

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Glycolysis as a therapeutic target for Parkinson's disease

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A drug licensed in the USA and Europe for the treatment of benign prostatic hyperplasia and hypertension might be neuroprotective in Parkinson's disease. This is the conclusion of a study that assessed the effects of terazosin across a range of experimental models of Parkinson's disease, and explored epidemiological associations in databases.[1] The report follows another study that identified that, in addition to blocking α_1-adrenergic receptors, terazosin acts on phosphoglycerate kinase 1 (PGK1) activity, increasing the product of glycolysis—ie, pyruvate.[2] This action has downstream consequences, increasing oxidative phosphorylation, mitochondrial activity,