

# Cure neurodevelopmental genetic disorders, please

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Dramatic, seemingly exponential advances have brought about much hope towards improving the efficacy of management of patients with conditions long-thought incurable, such as neurogenetic disorders. These advances have been both technological and conceptual. They result from refinements in the understanding of pathophysiology and intensive developments of approaches to compensate or bypass the critical failure that causes selected inherited disorders. Byzantine as they should appear to lay people or indeed to many clinical specialists and despite the barriers currently precluding their application, the names of these approaches have invested the language of increasing numbers of parents of children with neurodevelopmental genetic conditions. This leap from bench to dinner table is obviously allowed by the effectiveness and accessibility of communication technologies but it also reflects the emergence of the 'expert patient', which needs to be reconciled with professional understanding of disease [1]. This welcome evolution of parent-practitioner partnership has contributed to empowering parents in their own struggle for recognition and improved care. Within hours after the publication of a complex gene expression study on *Nature* website, we both received numerous e-mails from parents of children with Angelman syndrome to call our attention to it and to express hopes that a cure would be imminently available. Perchance a cure: *ay, there's the rub.*

Combined with communication technologies and parental empowerment, extension of the dynamics of translational research [2] has also initiated another type of partnership by fostering direct contact between parents and basic researchers. This is potentially a great source of both inspiration and progress to all. It may give parents a better understanding of the basic mechanisms underlying their child's condition and give researchers a better sense of 'real life' implications of what they study. But both parties stand the risk of treading this new arena unprepared. The issue of a conflict of interest may arise given the increasing role that parents advocacy groups have taken up in promoting research funding and the development of specific treatments. There is also a need for dispelling confusion: both parents and basic scientists must adapt their vocabulary. For example, it is deceptive to use the term 'cure' to characterize reversal of selected abnormalities in treated genetically engineered animal models of human disease.

With early detection and appropriate surgery, tumours can be physically cut out and not come back, i.e. cure. Similar cure can now be obtained through appropriate chemotherapy in many cases of cancer. Infective diseases also literally go away provided the causative organism can be killed. In diabetes, current treatment based on precise knowledge of the disorder mechanism may enable the patient to be well and participate fully although the condition is still there and will not go away. More unsure grounds are domains such as multiple sclerosis, where underlying mechanisms are not known precisely but certain medications have been shown to improve the condition or aspects of it, so that patients can be more functional than without these medications. These patients cannot be considered cured but perhaps managed to the best of current knowledge. The case of neurodevelopmental conditions is certainly more complex. Current understanding which founds developmental medicine and much of child neurology emphasizes the importance of maturational factors, experience-driven brain plasticity and the notion of critical periods that occur sequentially in a hierarchical order in embryonic, fetal and early postnatal life. Plasticity can imply windows of opportunity for

optimizing developmental trajectories as aimed for in ‘early intervention’ programmes, but it is constrained by these critical periods to a large extent. Therefore, there is currently no indication that neurodevelopmental genetic disorders might be cured by restoring normal gene expression, replacing or otherwise interfering with gene product, or bypassing the mutation altogether as we do not know (yet) how we could allow unconstrained brain plasticity to take place. This ominous barrier is evident in cases of obvious early disruption of brain organization, e.g. in tuberous sclerosis complex. But it would also be present in developmental neurogenetic conditions in which brain structure and function do not seem grossly abnormal in early infancy, such as fragile X, Rett or Angelman syndrome. The perspective might change when we gain better understanding of the role the concerned genes on brain development and function. Meanwhile, efforts into improving management need to rest very largely on improving physiological or adaptive functioning with a view to symptomatic relief and on individually-tailored habilitation programmes aimed at optimizing development, quality of life and participation.

The face of medicine and indeed that of our hopes for progress have very much brightened since Trudeau’s aphoristic call ‘to cure sometimes, to alleviate often, to support always’. Still Ronnie Mac Keith’s strong appeal to resist the ‘tyranny of the idea a cure’ when it is not possible and concentrate on alleviation and support [3] has acquired new meaningfulness precisely thanks to growing developments of better targeted therapeutics.

1. Dan B. The paediatrician’s role in support groups for rare diseases. *Acta Paediatr* 2008; 97: 1510-1.
2. Baxter P. Research priorities: Bless thee! Thou art translated. *Dev Med Child Neurol* 2008; 50: 323.
3. Mac Keith R. The tyranny of the idea of cure. *Dev Med Child Neurol* 1967; 9: 269-70.