Progress on polio in India

To the editor — Although it is good that the Indian military are to beat swords into calipers for children with residual paralysis from polio (see "Indian military scientists beat swords into plowshares," *Nature Med.* 2, 138; 1996), your article contained some inaccuracies. The old government leg braces are indeed too heavy, but for the last ten years they have been replaced by lightweight aids made from plastic guttering and polypropylene sheets at Non Governmental Organisations (NGO) such as Handicap International. For the simplest leg support, the cost is about US$3, considerably less than the $10 for the new device discussed in the article. The new device should therefore be compared to these aids, not to the obsolete iron braces.

Most estimates of polio incidence have suggested about 200,000 cases each year, in India, giving five million, not eight, over the last 25 years. Information from lameness surveys suggests that 65–75% of those lame can walk without aids and that about 15% are severely crippled and cannot walk. However, these were descriptions of ability, not need. How many of those able to walk without aids would do better with aids and how many will later suffer complications which could be avoided? Although the group may not have been typical, my analysis of 208 children requiring appliances at the RFFI Workshop in Pondicherry showed that for every 100 of these children, the requirements were for 110 short or long calipers, 5 hip calipers, 10 sticks and 37 crutches. Five children required operations.

Unfortunately, the provision of walking aids is no substitute for the care of the children with paralysis. In a study of 76 convalescent cases and 80 with residual paralysis 86% had avoidable sequelae[1]: "Limbs could have been preserved to a non-handicapping status if adequate and proper rehabilitation therapy was (provided) in the acute stage."

Furthermore, unless aids are fitted by trained technicians, deformities worsen. Children with contractures must have them corrected or alleviated. Unless these children are carefully monitored for exercises and use of aids, the contractures will recur and their surgery is wasted.

Finally, NGOs have found that waiting for children to be brought to a centre is not enough — physiotherapists and technicians must visit the villages to find the children. Parents must enforce exercises for these children, and plaster of Paris treatment of contractures should be encouraged. Research is urgently needed into why so few children wear their leg supports or return for physiotherapy and fitting.

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1. Srivastrava, R.K., Bhatnagar, S.K., Chand, N. & Mehrota, V. Paralytic poliomyelitis: rehabilitation point of view. *Indian Pediatr.* 22, 41–45 (1985).

Nonstop treatment of cystic fibrosis

To the editor — Howard and colleagues report that aminoglycoside antibiotics can induce the apparent readthrough of a number of naturally occurring premature termination codons (PTCs) in the sequence encoding the cystic fibrosis transmembrane conductance regulator (CFTR)[1]. The documented expression of full-length CFTR from the mutant cDNA-based expression constructs in the presence of aminoglycosides was associated with the emergence of cAMP-mediated anion efflux in transfected HeLa cell lines. On this basis, Howard *et al.* discuss the aerosolized delivery of aminoglycosides to the airway of patients with cystic fibrosis as a potential therapeutic strategy. Although we find the results quite intriguing, we suggest that there are many predictable obstacles standing in the way of a useful therapy.

All organisms that have been studied to date possess the ability to detect and degrade transcripts that contain a premature signal for the termination of translation[2]. This process of nonsense-mediated RNA decay (NMRD) appears to have a major nuclear component in mammalian cells. For many genes and mutations, the reduced abundance of cytoplasmic nonsense transcripts can be accounted for fully by a reduced abundance within the nucleus despite normal rates of transcription. NMRD appears to require intronic sequences and most cDNA-derived nonsense transcripts escape degradation[2]. Of particular interest is the observation that nonsense mutations can alter exon definition and utilization by the splicing machinery, a process clearly associated with the nuclear compartment and independent of the influence of ribosomes[3,4]. Yet, evidence exists that inhibition of translation initiation or elongation or the readthrough of PTCs by the introduction of suppressor tRNAs can abrogate NMRD, at least in part, in mammalian cells[2].

Notably absent from the study by Howard *et al.* is any consideration of the potential for PTC-mediated perturbation of transcript stability or processing by CFTR nonsense mutations *in vivo*. The use of intronless minigenes precludes the potential to appreciate any relevant effects in their system. Furthermore, the *in vivo* effects of the two CFTR mutations used in this study (G542X and R553X) have been analyzed extensively. Both mutations are associated with a severe reduction in transcript level, less than 5% of that derived from the other allele in heterozygous individuals[5,6]. Also, R553X has been shown to result in the skipping of the exon containing the nonsense mutation during pre-mRNA processing[7]. In the light of the vagaries concerning the mechanisms of NMRD and aminoglycoside-induced readthrough of PTCs, it is impossible to predict the consequence of their potential interactions. We anticipate that no clinical benefit will be derived from the provision of the ability to readthrough nonexistent or centrally deleted nonsense transcripts.

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Bedwell and colleagues reply — The abundance of many mRNAs containing premature stop mutations is reduced when compared to the corresponding wild type mRNA. Various models have been proposed to explain this observation, and it is possible that nonsense codons within