The mills of God grind slowly. The medical profession are not far behind. It is almost 40 years since Drachman et al. [1] in an open study of 14 patients with Duchenne dystrophy, aged 3–10 years, for periods ranging from 1 to 28 months, concluded that steroids might have some palliative benefit, and that further studies were needed. Some 14 years later Brooke and his colleagues [2] took up the challenge and showed in a multicentric study of 33 patients, aged 5–15 years, (12 of whom had a ready lost ambulation), a definite improvement in muscle function on 1.5 mg/kg/day of prednisone, compared with the natural history of their 170 historical controls in earlier studies. At the same time DeSilva et al. [3] showed long-term benefit in some of the original Drachman cases, using age of loss of ambulation as the only criterion for assessment. They concluded, however, that the relatively short-lived beneficial effect on the muscle strength was outweighed by the not inconsiderable side effects of prolonged steroid therapy, and did not feel able to recommend steroids as a general long-term therapy for muscular dystrophy.

Brooke and his colleagues [4] then went onto a randomized, double-blind, placebo-controlled trial of 103 boys aged 5–15 years, at two dosage levels of 1.5 and 0.75 mg/kg/day, over a 6 month period and found a comparable increase in muscle strength in the two prednisone groups at 1, 2 and 3 months, after which it leveled off, whereas the control group showed a steady loss of strength similar to the natural history.

When Mike Brooke reviewed their cumulative data at the International Muscle Congress in Munich in 1990 [5], I was struck by the regular increase in muscle strength after initiation of therapy, followed by a plateau, and wondered whether pulsed therapy might produce similar results and avoid the not inconsiderable side effects, which they still considered at that time a constraint on recommending the treatment [6].

I tried a schedule of 10 days of therapy at 0.75 mg/kg/day at the beginning of each month, which I thought would be long enough to get the benefit, but short enough to safely stop without tapering. A pilot study in 32 ambulant Duchenne boys, including orthoses, aged 6–14 years, showed a definite benefit which was sustained for about 6 months and then showed some decline [7].

Many patients also commented on a decline again in function around day 20 onwards each month. After this trial it was decided to switch to a regime of 10 days on (Monday–Wednesday) and 10 days off (Thursday through Sunday, to make it easy for the parents). This regime essentially halved the load of steroid and we hoped would reduce the troublesome side effects of continuous therapy.

A further study of early cases under 5 years of age, with measurable deficits in function, showed a much more dramatic effect of the intermittent steroids (at 0.75 mg/kg/day) and in some cases apparent resolution of all the clinical signs of Duchenne dystrophy and achieving a full score of 40/40 on the Hammersmith Motor Ability score [8].

In a follow-up of four early cases for at least 30 months [9] the response seemed to be sustained for 3 or 4 years, after which there was a fairly rapid decline. There were no obvious extraneous factors and we wondered if this might coincide with the onset of the normal growth spurt. In earlier natural history studies of Duchenne dystrophy, the median for loss of ambulation was around 9 years, which seemed to relate to the normal growth spurt, with change in body dimensions but no commensurate increase in muscle power [10].

There has been a tendency to dismiss the serious side effects of continuous steroid therapy but in the early years these were considered a major contraindication to the use of corticosteroids in Duchenne. At the time of the first ENMC workshop on steroid treatment in Duchenne in 1996, there were only 7 centres in Europe with experience in the use of steroids in Duchenne, including only one in the UK [11]. By the time of the second workshop in 1999 there were numerous centres and...
within the UK potentially 15 centres prepared to collaborate in a multicentric study [12].

At the next ENMC workshop in 2004 [13] it was decided to go global and undertake a very extensive multinational, multicentric, randomized controlled trial, comparing continuous with intermittent (10 days on/10 days off) prednisone therapy. A further 9 years have passed and this trial is just starting and will presumably take several years to complete.

Meanwhile in the UK several centres have continued with their program of prednisolone therapy and adopted an equipoise approach, discussing with the families the two options, daily versus 10 days on/off, with benefits and side effects, and giving them the choice of which regime to opt for.

Ricotti and her colleagues [14] have recently reviewed the benefits and side effects in 360 boys, aged 3–15 years, with confirmed Duchenne dystrophy, in 15 neuromuscular centres in the UK. Of these 136 were on daily prednisolone therapy and 154 on intermittent. A further 70 switched from one regime to the other. The median loss of ambulation was 12 years in the intermittent and 14.5 years in the daily. A statistical multilevel model comparison of the two regimes showed them running parallel till after 7 years and then diverging. Moderate to severe side effects were significantly higher in the continuous than the intermittent therapy group, including stunted growth and increased BMI.

This raises the question as to whether the apparent benefit of longer ambulation in the continuous therapy group could at least in part be due to the major side effects of long term continuous steroid therapy with early closure of epiphyses and stunting of growth and absence of the normal growth spurt, which seems to be a major factor in the timing of the loss of ambulation.

It needs powerful statistics to draw a regression line through a snowstorm ([14]; fig. 3). However it should be possible, using height as a variable, to see if there is a correlation between height and loss of ambulation, or conversely between stunting of growth and continued ambulation.

Perhaps what is now needed is not further randomized controlled studies, which are likely to produce the same results, which have already become apparent in the many observational studies over the past 20 years, but to consult the patients and their families with the choice of two regimes and their relative benefits, in the face of the potential side effects, and get a clearer picture of their main priorities and objectives.

It might be argued that this has already been done in the current study, but looking at the data on the distribution of cases in different centres, some are certainly more equipoised than others, and a few centres have the vast majority of their cases in one or other group, which would more likely reflect the bias of the clinician rather than the choice of the patient.

Since there is well documented evidence of substantially more response to corticosteroids in early cases, it would also be worth focusing on younger boys, between the ages of say 3 and 5 years, for commencing therapy, and potentially getting the maximum benefit.

References