Longitudinal growth rate following slow physeal distraction

The proximal tibial growth plate studied in rabbits

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Studies in animals by de Bastiani et al. (1986) on leg lengthening by physeal (growth plate) distraction have shown that the integrity of the growth plate can be preserved intact if slow rates of distraction are employed. Clinically, however, this technique has been restricted to the period shortly before skeletal maturity, due to uncertainty about the behavior of the growth plate following distraction.

We conducted 2 studies. 11 immature rabbits used in a study on the normal growth at the proximal tibial physis established that the growth rate was unchanged with transfixing K-wires in the epiphysis. The normal growth rate of the proximal physis of the tibia decreased with age and was expressed as a quadratic function, G_n (mm/day) = 0.44–0.002 age (days). At 6 weeks of age, the growth rate was 0.33 mm/day, slowly decelerating to a rate of 0.15 mm/day by the 16th week. In the lengthening study, to determine whether the growth plate would maintain a normal rate of growth following slow distraction, a custom-made bilateral distraction device was applied to the proximal tibial epiphysis of 32 immature rabbits aged 6 weeks and weighing approximately 500 gm. The growth behavior of the growth plate following 2, 3 and 4 weeks of distraction was studied. The rate of distraction was set at 0.5 mm/day. The mean amount of distraction achieved was 8.5 mm, 11.3 mm and 14.6 mm resulting in a mean 'net' increase in length as compared to the experimental control after the distractor was removed amounting to 3.0 mm (55% of the control growth), 3.6 mm (47%) and 4.2 mm (40%), respectively. Subsequent serial measurements, up to 13 weeks postdistraction, showed no significant change in the discrepancy between the length of the tibia and the growth rate at the proximal tibial epiphysis and between the distracted and the contralateral controls in all 3 groups. Our findings suggest that the proximal tibial growth plate in the rabbit would maintain a normal growth rate after slow physeal distraction for periods up to 4 weeks.

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Ring (1958) was probably the first to produce limb lengthening by applying traction across the growth plate (physis). He was uncertain whether this was caused by accelerated growth or rapid healing of a fracture separation through the plate. Limb lengthening in animals by distraction of the growth plate (distraction physiolysis) has since been described by many authors (Ilizarov and Soybelman 1969, Zavyalov and Plaksin 1968, 1969) who were the first to describe its clinical application. These early results showed that significant early increase in length could be achieved, but the subsequent growth plate viability and potential for further growth were jeopardized.

Sledge and Noble (1978) and Noble et al. (1982) applied constant tension to the distal femoral physis of rabbits and showed that lengthening could be achieved without fracture and with a reasonable degree of predictability, using lower forces. Histological examination of the growth plates following distraction revealed an overall increased thickness, most marked in the proliferative and hypertropic zones. Their specimens showed marked hyperplasia and hypertrophy at these sites, suggesting an enhancement of the cellular aspects of the growth process. De Bastiani et al. (1986a, b) confirmed these changes and their findings indicated that the growth plate regained morphology and structure and retained its function when distraction ceased. However, differences of opinion over the reported reduction in longitudinal growth in several other clinical and experimental studies (Ring 1958, Letts and Meadows 1978, Fjeld and Steen 1988, 1990, Monticelli and Spinelli 1981a, b) as to whether epiphyseal distraction has very little, if any, effect on the postdistraction growth period and growth rate (De Bastiani et al. 1986a, b, Fishbane and Riley 1978, Sledge and Noble 1978) has led clinical

Figure 1. Lengthening study. Serial radiographs of the effect of distraction on the longitudinal growth over the period of assessment. In this case the limb was distracted up to 4 weeks (group III) and growth observed up to 12 weeks postdistraction.

workers to restrict the use of this technique to the period shortly before skeletal maturity.

We investigated whether or not the proximal tibial growth plate in the immature rabbit would maintain a normal growth rate after different periods of physeal distraction.

Animals and methods

Normal growth study

This study was carried out to ascertain the normal growth rate in rabbits and whether the growth activity of the physis was influenced by the implantation of Kirschner (diameter 1.4 mm) wires in the epiphysis. 11 laboratory-bred New Zealand white rabbits aged 6 weeks and weighing an average of 500 g were used for this part of the study.

For each specimen, a single K-wire was implanted in the diaphysis on the left tibia to act as a marker for monitoring the normal rate of growth. On the right tibia, one K-wire was implanted in the epiphysis and another in the diaphysis at the same level as the left tibia. This was used as a model for the control limb in the lengthening study. Radiographs were taken immediately after the operation and at intervals of 1 week thereafter. Incremental length measurements were then recorded to monitor the growth of the normal limb (ΔL_n) and experimental control limb (ΔL_e) at the proximal tibia postoperatively.

A separate pilot study was carried out to determine the optimal rate of distraction, which was sufficiently fast to achieve lengthening of the rapidly growing immature rabbit, while maintaining a low risk of fracturing the plate. This rate was established as 0.5 mm/day.

Lengthening study

32 laboratory-bred New Zealand white rabbits aged 6 weeks and weighing between 480 g and 520 g were used in this part of the study. K-wires were implanted, one in the proximal epiphysis and one in the diaphysis of both tibiae. A custom-made bilateral configuration type distractor was then assembled on the right tibia, while the left tibia acted as an experimental control to indicate the normal rate of growth at the proximal tibial physis.

Experimental groups. Physeal distraction was performed at a rate of 0.5 mm/day. For group I (n 6), the distraction was for a period of 14 days, group II (n 15) a period of 21 days and group III (n 11) a period of 28 days. In each group after the distraction period, the distractor was held in a fixed neutral position for 3 days (neutralization period). This was found necessary to prevent any collapse of the metaphysis and also to allow the cortices to mature. The distractor was subsequently removed and the tibia was allowed to grow.

All operations were carried out under ketamine (50 mg/kg) and diazepam (5 mg/kg) anesthesia with pethidine (10 mg/kg) given postoperatively. After the operation, prophylactic intramuscular ampicillin (10 mg/kg) was given for 5 days.

Longitudinal growth and growth rate. Serial radiographs were taken, starting immediately after the operation and at 1-week intervals, employing a jig which enabled the tibiae to be held at a fixed distance against the x-ray plate, thus minimizing the error due to magnification of projection (Figure 1). A standard metal template placed in the exposure area acted as a measure to correct for magnification. A baseline radiograph was taken at the time of operation. This would also ensure that the proximal K-wire was correctly placed and would not involve the growth plate. Incremental lengths of the control limb (ΔL_e) and the distracted limb (ΔL_d) were then recorded as the absolute postoperative longitudinal growth at the proximal tibia. All measurements from the radiographs were in mm, to the nearest 0.05 mm. The mean absolute longitudinal growth was plotted against the age of the rabbit in days, postoperatively. A regression analysis and a quadratic growth model (Eqn. 1) were used to estimate the individual growth differences between the control and the experimental limbs and to model the growth rate.

$$\Delta L_i = k_0 + (k_1)\, a + (k_2)\, a^2 \qquad \text{(Eqn. 1)}$$

where ΔL is the mean longitudinal growth (mm) measured postoperatively, i denotes the various conditions (n normal, e expermental control, d distracted limb), a is the age of the rabbit (days), and k_0, k_1 and k_2 are parameters of the model. The growth rate, G_i (mm/day) with respect to the age of the rabbit (days), was then estimated by the following relationship

$$G_i = \frac{d(\Delta L_i)}{da} \qquad \text{(Eqn. 2)}$$

Substituting Eqn. 1 for Eqn. 2 and differentiating with respect to a, we then obtain

$$G_i = k_1 + (2k_2)\, a \qquad \text{(Eqn. 3)}$$

The parameters in Eqn 1 and 3 can be interpreted as growth from birth until just before operation (k_0), initial growth rate at birth (k_1) and half the age-dependent growth deceleration (k_2). The age of the rabbit was used as a reference, as it allowed us to compare the postdistraction growth rate to the normal growth rate of the rabbit.

Statistics

A two-way analysis of variance (ANOVA) and the paired Student's t-test were used to compare the mean incremental length or longitudinal growth discrepancies between the control and the normal tibia in the normal growth study and the distracted and control tibia for each group in the lengthening study with increasing postoperative week. Regression analysis using a quadratic curve estimation was used to model the longitudinal growth at the proximal tibia against the age of the rabbit. The mean longitudinal growth rates in the control limbs in groups I, II and III were also tested against one another, using a two-way ANOVA. A 0.05 level of significance was used in all tests.

Results

Normal growth study

The longitudinal growth after insertion of pins was plotted against the age of the rabbit in days (Figure 2). The control tibiae with pins inserted at the epiphysis and the tibiae without epiphyseal pins showed a postoperative mean discrepancy in length of 0.27 mm

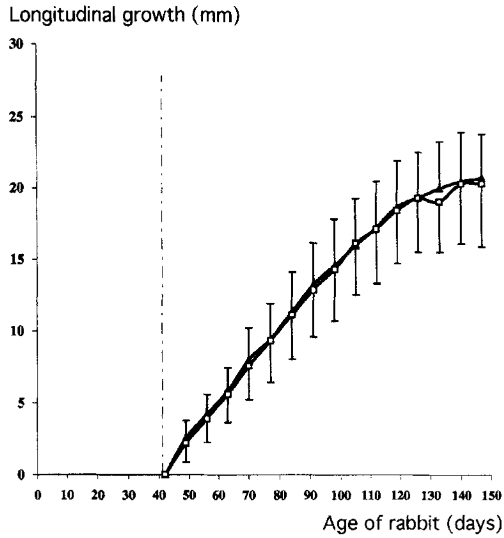


Figure 2. Mean longitudinal growth at the proximal tibia in relation to the age of the rabbit in days, comparing the normal limb, ΔL_n (▲), to the control limb, ΔL_e ( ), after the insertion of a K-wire through the epiphysis at 42 days (broken line).

(< 0.5 % retardation) ($p > 0.5$, ANOVA). From the quadratic regression analysis curve fit (Eqn. 1 and Eqn 3), the following expressions for the longitudinal growth and the growth rate with respect to the age, a, was derived.

Normal (without k-wire inserted at the epiphysis)
Longitudinal growth,
$\Delta L_n = -16.3 + 0.44\, a + 0.0012\, a^2$ (Eqn. 4)
($r^2 = 0.867$, $p < 0.001$)
Growth rate, $G_n = 0.44–0.0024\, a$ (Eqn. 5)

Control (with k-wire inserted at the epiphysis)
Longitudinal growth,
$\Delta L_e = -16.7 + 0.44\, a -0.0013\, a^2$ (Eqn. 6)
($r^2 = 0.826$, $p < 0.001$)
Growth rate, $G_e = 0.44– 0.0024\, a$ (Eqn. 7)
where r^2 is the coefficient of determination for the linear regression analysis.

Lengthening study

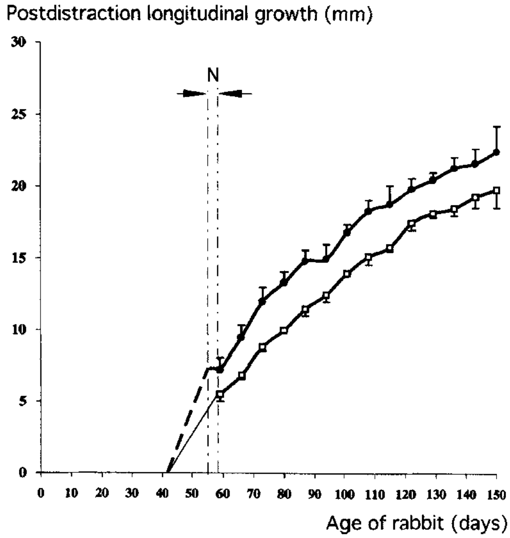
Complications. 9 cases of complications were seen and these were excluded from the study (Table 1). Of these, 4 were cases with little, if any, growth postdistraction, strongly suggesting damage to the growth plate. Net increase in longitudinal length in these cases was found to constitute more than in the uncomplicated limbs, indicating that the distraction rate was higher (about twice the normal growth during the first 2 weeks of distraction).

The mean original length of the tibia of a 6-week-old rabbit was 54 (SD 3.0) mm. The amount of

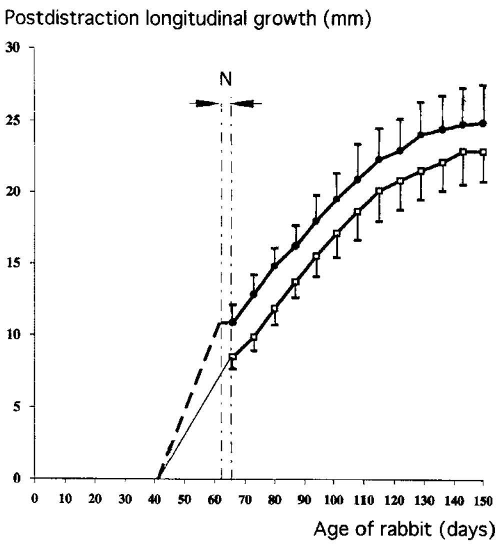
Table 1. Complications, excluded from the study

Group	Complication	No. of specimens	No. of specimens remaining in the group
I	Epiphysiolysis	2	3
	Fracture	1	
II	Epiphysiolysis	2	
	Collapse of metaphysis	2	9
	Local sepsis	1	
	Valgus deformity	1	
III	–	–	11

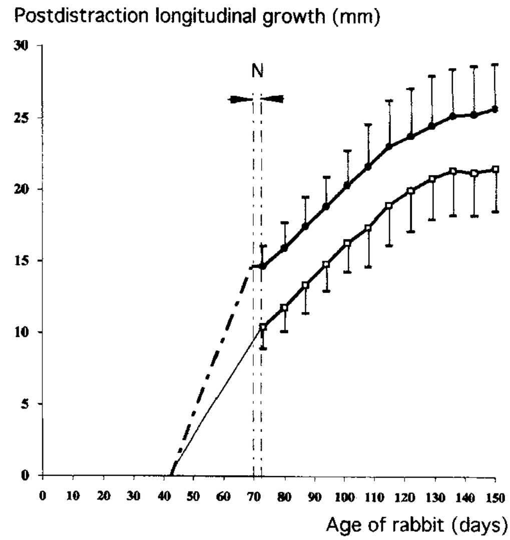
Figure 3A–C. The mean postdistraction longitudinal growth at the proximal tibia (mm) is plotted against the age of the rabbits in days. Group I, II, and III had a 2-, 3-, and 4-week distraction period follow by a 3-day neutralization period (N), ΔL_e longitudinal growth in the control limb (□) and ΔL_d longitudinal growth in the distracted limb (●). Distraction was set at 0.5 mm/day.



A. Group I. 2 weeks distraction



B. Group II. 3 weeks distraction.



C. Group III. 4 weeks distraction.

Table 2. Distraction and growth of the contralateral limb measured on the day when the distractor was removed after a period of neutralization. Mean SD (95% confidence interval of the mean)

Group	n	Distraction ΔL_d (mm)	Growth in the control limb ΔL_e (mm)	Length discrepancy ΔL_d-ΔL_e (mm)	% Length discrepancy $100*(\Delta L_d-\Delta L_e)/\Delta L_e$
I (2 wks)	3	8.5 0.85 (6.4–10.7)	5.5 0.41 (4.3–6.7)	3.0 1.00 (0.5–5.5)	55%
II (3 wks)	9	11.3 1.18 (10.9–12.8)	7.7 0.82 (7.0–8.3)	3.6 1.85 (2.7–5.6)	47%
III (4 wks)	11	14.6 1.37 (13.7–15.6)	10.4 1.46 (9.4–11.4)	4.2 0.96 (3.6–4.9)	40%

lengthening produced by the distraction process and the simultaneous growth of the control limb on the day of removal of the distractor after a period of 3 days of neutralization are summarized in Table 2.

Postdistraction discrepancy in longitudinal growth. The postdistraction increase in length (or longitudinal growth) was plotted against the age of the rabbit in each group (Figure 3). A two-way ANOVA

Table 3. Parameters for Eqn 1 and Eqn 3. Mean (95% confidence interval of the mean). r^2 is the coefficient of determination of the non-linear regression analysis

Group	Parameters for Eqn 1 and Eqn 3			Regression analysis
	k_0	k_1	k_2	r^2; (p-value)
I Distracted limb	−7.01 (−11 to −3.5)	0.35 (0.27 to 0.43)	−0.0010 (−0.0014 to 0.0006)	0.98; $p < 0.001$
Control limb	−9.80 (−12 to −7.8)	0.34 (0.30 to 0.38)	−0.0009 (−0.0014 to −0.0007)	0.98; $p < 0.001$
II Distracted limb	−11.4 (−17 to −5.6)	0.47 (0.35 to 0.59)	−0.0015 (−0.0021 to −0.0010)	0.84; $p < 0.001$
Control limb	−14.8 (−20 to −9.8)	0.46 (0.35 to 0.57)	−0.0015 (−0.0020 to −0.0010)	0.87; $p < 0.001$
III Distracted limb	−9.18 (−19 to 0.63)	0.45 (0.29 to 0.65)	−0.0014 (0.0024 to 0.0005)	0.64; $p < 0.001$
Control limb	−14.5 (−23 to −5.5)	0.47 (0.29 to 0.65)	−0.0014 (0.0024 to 0.0007)	0.73; $p < 0.001$

and the paired Student's t-test established that the mean discrepancy in longitudinal growth between the distracted limb and the control limb at the proximal tibia for each week postdistraction did not change significantly in all 3 groups ($p = 0.2$).

Experimental control limbs in groups I, II and III. The mean longitudinal growth (ΔL_e) of the control limbs in groups I, II and III were found to be not significantly different at each postdistraction week ($p > 0.5$, ANOVA).

Postdistraction longitudinal growth and growth rate. Using a quadratic regression analysis curve fit, the expressions for the longitudinal growth (Eqn. 1) and the growth rate (Eqn. 3) were obtained in the distracted limb and the control limbs in each group and the parameters in both equations (k_0, k_1, k_2) are summarized in Table 3. The postdistraction growth rates (G_d) of the distracted limb were found to be similar to the postdistraction growth rates (G_e) of the contralateral control limb in all 3 groups. The growth rates were plotted against the age of the rabbit (days) and compared to the normal growth rate, as determined in the normal growth study (Figure 4).

Discussion

To make observations for an acceptable period it was necessary to use small, immature and very rapidly growing animals. This inevitably leads to lower limits of safety and a higher rate of complications. The normal growth was represented as a quadratic function of age and growth rate was expressed by a linear function ($G_n = 0.44–0.0024a$) having a decelerating factor with age. We chose a quadratic function over the logarithmic or power function for the longitudinal growth to allow us to model the growth rate as a simple linear function.

The postdistraction growth rates of the distracted limb were observed to be similar to those in controls in each group and the decelerating factor with age was not different from the normal growth rate. The fast growth of the immature rabbit made it essential that the neutralization period was kept to a minimum in order to preserve the additional length. However, we had to allow the cortices sufficient time to mature and avoid collapse of the metaphysis. How the duration of the neutralization period affects the postdis-

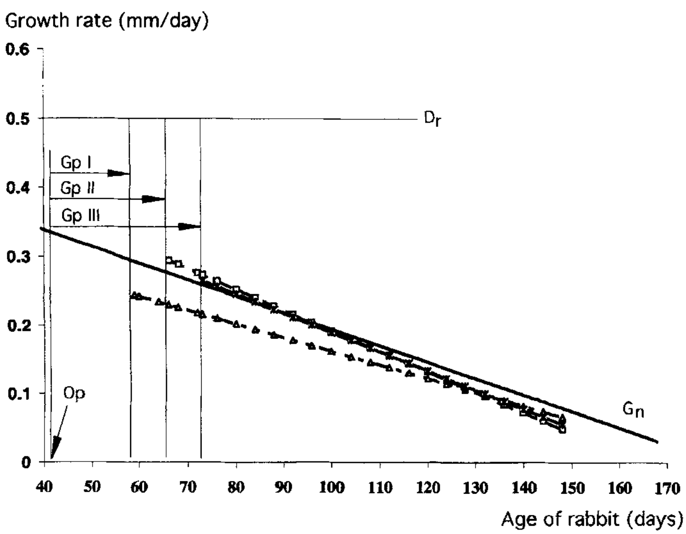


Figure 4. The postdistraction growth rate (mm/day) of group I (▲), group II (□) and group III (✱) plotted against the age of the rabbit, *a* (days) and compared to the normal growth rate (G_n) of the proximal tibial epiphysis ($G_n = 0.44 - 0.0024a$). The distractor was inserted at the operation day (Op) and removed after distraction and a 3-day neutralization period (horizontal arrows). The distraction rate (D_r) was 0.5 mm/day

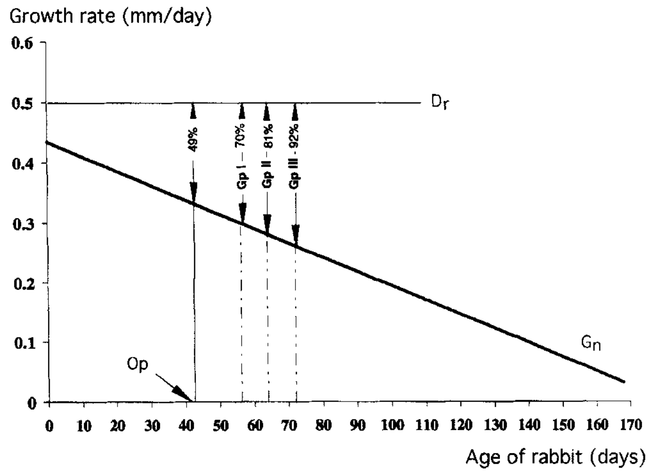


Figure 5. Normal growth rate (G_n) in mm/day ($G_n = 0.44–0.0024a$; a = age in days of rabbit) of the proximal tibial epiphysis of the rabbit compared to the fixed distraction rate (D_r) of 0.5 mm/day over the period of postdistraction up to maturity. Op = operation day.

traction growth potential needs further study.

In rabbits, the normal growth rate at 6 weeks of age was 0.33 mm/day. Use of a distraction rate of 0.5 mm/day would give a rate faster than 149% of the normal growth potential between a = 42 days and a = 49 days (Figure 5). Fixing the rate throughout the distraction period may not be entirely satisfactory because the normal rate of growth changes with age. After 2 weeks of distraction (8-week-old rabbit) the distraction rate would be as fast as 170% of the normal growth rate, increasing to 181% and 192% for the subsequent 2 weeks. This could explain why some workers noted conflicting results of growth retardation and physiolysis, when using a fixed rate of distraction or higher rates of distraction at a later period or for longer periods which leads to larger amounts of distraction over the normal. This would increase the load across the growth plate which causes fracture. If longer periods of distraction are required, it may be necessary to adjust (reduce) the distraction rate with increasing age to avoid having a distraction rate faster than 200% of the normal growth rate.

Our study analyzes the longitudinal growth and the growth plate. Although the sample size was small, the study shows that 1) the growth activities did not change significantly when a small K-wire was implanted through the proximal tibial epiphysis by percutaneous pinning, 2) for immature rabbits, provided fracture of the growth plate does not occur, slow physeal distraction up to a period of 4 weeks does not significantly affect growth.

Physeal distraction as a method for correcting leg length inequality has many advantages over the other methods currently available (Paley 1988), since it is minimally invasive, hospitalization is short and the child's schooling need have little interruption. However, we caution that the rate of distraction and the period of neutralization should be tailored to the age, sex, rate of growth in the contralateral limb, and the cross-sectional area of the growth plate which is involved in the distraction. Furthermore, although we found that the growth rate returns to normal, the technique is difficult with significant risk of growth plate fracture and this, of course, is a major problem in the clinical distraction of very young children.

Our results suggest that the rate of distraction should decelerate with the neutralization period adjusted. However, it is important to note that the relative growth rates in the rabbit are higher than in larger mammals, like humans, therefore further clinical studies are needed to tailor the distraction rate for children. Monitoring with strain gauges would greatly minimize the risk of physiolysis. Jones et al. (1989) found that using fixed rate distraction, all 10 epiphyses in their study separated within 32 days. They felt that in order to avoid failure across the growth plate, the stress should be maintained at less than 0.15 MPa. The work of Nobel et al. (1982) would thus become important, since it might be much easier to minimize complications if the tension force or perhaps even if tension stress was chosen to control the distraction rather than strain or a fixed rate of distraction, provided the strength of the epiphysis is taken into account (Hirasawa et al. 1994).

How the accelerated growth is to be achieved during distraction and whether mechanical force stimulates or inhibits proliferating activity at the growth plate is a subject of some speculation (Trueta and Amato 1960, Hert 1969, Bourret and Rodan 1976, Brighton 1978, Jones et al. 1989, Alberty et al. 1990, 1993, De Pablos, Jr. and Canadell 1990, Kenwright et al. 1990, Elmer et al. 1992, Alberty 1993). More work is required to understand fully the response of the growth plate to mechanical forces and to realize fully the merits of slow physeal distraction. De Pablos' and Canadell's (1990) prudent advice is to note 2 limitations when doing animal experiments. First, the difference in the growth potential of animals to humans and secondly, the fact that the animal models used so far have all been based on distraction of a normal growth plate. Our task is to establish the correct regime for distraction and future studies should be focused on more sophisticated analysis and the best way to extrapolate experimental data to predict the results for use in younger children.

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