

Model of normal prepubertal growth

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Abstract

Growth over the short term is a highly complex non-linear process. Contrasting models of short term growth have been proposed which include periodic growth cycles versus abrupt growth spurts with intervening growth arrest ('saltation and stasis'). The variability of short term growth has been characterised from a study of 46 healthy prepubertal children measured three times a week over one academic year using a combination of descriptive statistical approaches and regression modelling. Growth in childhood over one year is represented by a biphasic process comprising three to six unpredictable growth spurts, each of mean length 56 days (range 13-155 days), separated by periods of stasis (less than or equal to 0.05 cm height increment over more than seven days), each lasting a mean of 18 days (range 8-52 days) and accounting for at least 20% of the period of observation. This is superimposed on a strong seasonal trends in growth with a declining growth rate over the autumn months reaching a nadir in midwinter, followed by a growth spurt in the spring. Human growth over short periods is therefore a discontinuous, irregular, and unpredictable process.

(*Arch Dis Child* 1996;75:427-431)

Keywords: growth, prepubertal, mathematical models.

Conventionally, growth in childhood is considered to be a relatively smooth and orderly process: rapid growth in infancy gives way to 'linear' growth in mid-childhood, finally culminating in the adolescent growth spurt. The familiar shape of the childhood growth curve was first shown by Count Philibert de Montbeillard in the eighteenth century from biannual measurements of his eldest son from birth to maturity.¹ This early work also illustrated diurnal variations in stature and seasonal fluctuations in growth and was the first demonstration of the discordance between short and long term growth. In fact, the more closely that growth is studied, the more irregular it appears.² This important observation greatly complicates the study of short term growth. Additionally, measurement error is such that even in experienced hands the 95% confidence limits for a single height measurement are estimated at ± 0.5 cm, despite using a standard measurement technique.³ Consequently, discerning the true pattern of growth becomes very difficult.

Studies have attempted to address this key issue by frequent measurements on a small numbers of subjects. For instance, weekly height measurements taken by parents on 10 short children were found to be described by linear trends.⁴ In contrast, weight gain in growth retarded infants,⁵ catch-up growth in infants with treated coeliac disease,⁶ and growth in normal children^{7,8} and those with cystic fibrosis⁹ may be described by 10 day, 60 day, and annual cycles, respectively. Using the knemometer to obtain highly accurate weekly measurements of the lower leg, minigrowth spurts occurring at 30-55 day intervals have also been described.¹⁰ In contrast, accurate measurements of limb growth in rabbits using metal pins inserted into the tibia¹¹ have shown growth to be a continuous process. All height gained in childhood has been proposed to occur in irregular growth spurts or saltations over one day with intervening periods of no discernible growth (stases) based on studies of infants¹² and one adolescent child.¹³ It has also been suggested that growth may be proceeding in a chaotic manner.² There is therefore a wide range of putative models of human growth.

Our aim in this study has been to define short term growth in a large cohort of normal children by mathematical techniques that do not impose an artificial form to the growth pattern. By gaining an insight into normal growth we may anticipate a better understanding of pathological growth and the influence of treatment, so that growth promoting treatments may be used more appropriately and effectively.

Subjects and methods

SUBJECTS

We examined the growth of 46 healthy prepubertal schoolchildren (18 boys and 28 girls) aged 5-8 years using height measurements taken three times a week over one academic year. The children were not measured in school holiday periods. The children were volunteers and parental consent was obtained for the study. Measurements were conducted by two observers using a free standing Magnimetre (Raven Instruments) calibrated on each occasion with reference to a machined metre rod. To minimise the effect of posture, activity levels, and the normal diurnal variation in height the children were measured at the same time of day on each occasion and a standard 'stretch' technique was used.³ To accustom the children and the observers to the procedures there was a three week 'run-in' period at the end of the preceding school year. The SD of the differences between 'blind' triplicate measurements of the same 25 children was 0.13 and

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Accepted 19 July 1996

0.15 cm, respectively, for the two observers, comparable with the SD in other intensive growth studies.^{2,13} The mean (SD) interobserver difference was 0.04 (0.04)cm.

The mean height SD score was 0.0 (range -3.4 to +2.8) according to 1990 UK standards.¹⁴ Heights were distributed evenly across the centiles with one child's height above the 98th centile and one below the 0.4th centile. Annualised growth velocities were all within the UK normal range (mean 7.5 cm/year; range 4.8–8.9 cm/year).¹⁵ Over the period of study there was a non-significant mean increment in SD score of 0.29 (range -0.14 to +0.48). Observations were made on 94 occasions, the median for one subject being 89 (range 60–94).

STATISTICAL ANALYSIS

Analysis of serial height differences

Serial increments in height scaled by the intervening time interval (in effect, empirical estimates of the daily height velocity) were derived for each child. If growth is a linear process with uncorrelated, normally distributed measurement errors, with a mean of zero and constant variance, then the serial height differences would conform to a Gaussian distribution with a mean corresponding to the daily growth rate and variance proportional to measurement error. In contrast, a saltatory growth process would be predicted to result in either a single positively skewed distribution or two distinct distributions, one representing height stasis, the other rapid growth.^{11,16,17} Normality of the histograms of height differences for each individual and for the group as a whole was assessed using the Shapiro-Wilk test. The Durbin-Watson test of linearity was also applied to determine the presence of linear growth trends. A distribution consisting of a mixture of two normal distributions with unequal means and variances was fitted to the scaled height increments using the maximum likelihood technique.¹⁸ This technique did not take into account serial correlation between measurements.

Analysis for the presence of saltations

A modified process control technique to look for abrupt changes in stature was used. In each child the changes between successive pairs of height differences scaled by the time interval (that is changes in the empirical velocities) were compared with the null distribution, which assumed that the mean change was zero. No assumption of normality was made in estimating this null distribution. A smoothed bootstrap resampling technique¹⁹ was used to take into account the presence of correlation between successive pairs of measurements and also incorporated a monotonicity constraint that did not allow loss of stature. This would reduce the spurious identification of an abrupt change in velocity attributable only to measurement error. We also considered that height shrinkage due to soft tissue or bone compression, or both, although recognised over one day by conventional height measurement,² would not be a critical factor

over longer measurement intervals. The incidence of significant abrupt velocity changes was assessed by identifying the number of times that the difference in successive height increments exceeded critical values determined at both the 1 and 0.5% levels for each individual. These critical values (1% level, mean 0.282 cm/day, range 0.159–0.444 cm/day; 0.5% level, mean 0.300 cm/day, range 0.165–0.467 cm/day) took into account the variation in stature measurement between individuals and were an indirect reflection of the error variance.

Non-parametric regression modelling

To obtain a better estimate of growth and growth velocity as a function of time, locally weighted, least squares kernel regression was used,²⁰ with a bandwidth of 49 days for the height regression and 60 days for the velocity regression: bandwidths were determined by a predicted squared error criterion.²¹ This is a non-parametric technique and hence does not impose a form to the regression estimate, unlike a linear, polynomial, or step function. This technique assumes that for each child height is being modelled as a smooth function of time, while accounting for measurement error. We arbitrarily defined a growth stasis as any period in which an increment derived from the smoothed heights of less than or equal to 0.05 cm over seven or more days occurred (compared with the mean growth rate of 0.2 cm/week). Data were expressed as number and duration of stasis.

Growth spurts were identified by inspection of the peaks in each individual's growth velocity curve. Mean peak length (days) and mean interpeak interval (days) with ranges were calculated for the whole group. If the velocity curve fell below 0.007 cm/day (less than or equal to 0.05 cm over seven or more days), then these periods were not included in the estimation of peak length.

Results

Examination of the frequency histogram of scaled height differences for each individual revealed a peaked distribution in all instances. The Shapiro-Wilk test confirmed that for 45 of 46 children these data were not normally distributed. Furthermore, a linear growth pattern was not found to be appropriate in all 46 children. For the whole group the serial height differences were best described by a composite of two normal distributions (fig 1), with one narrow distribution centred close to zero and the other wider distribution centred at 0.046 cm/day. This analysis suggested that growth was comprised of two distinct phases, one of stasis or near stasis, and the other of continuous growth over a wide range of growth velocities. Nevertheless, inspection of the height data for the whole cohort indicated that each child did have occasional jumps in height compatible with saltations.

Using the modified process control technique at the 1% critical value, 41 of the 46 children showed one or two abrupt changes in growth velocity (30 had one, 11 had two).

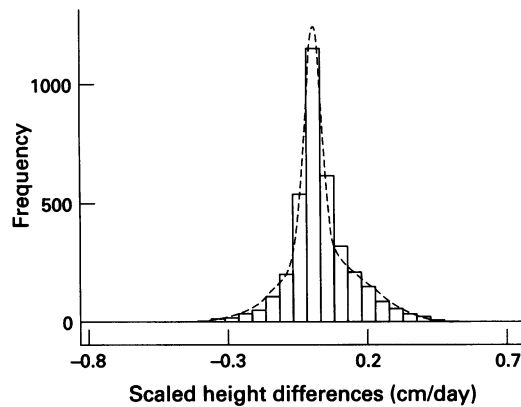


Figure 1 Histogram of the scaled height differences ($n = 3674$) from the complete cohort ($n = 46$). The distribution of height differences for the whole group (and for individual children) was not normally distributed. The composite curve that best fits these data is shown: it is comprised of two normal density curves which are defined by (i) $0.423 \times N(0.002, 0.001)$, and (ii) $0.577 \times N(0.046, 0.024)$, where $N(m, v)$ denotes a normal density with mean m and variance v .

These saltatory increments varied in magnitude from 0.167 to 0.495 cm/day (mean 0.32 cm/day). At the 0.5% level, 25 children had one abrupt change in velocity and five had two, with a mean saltatory increment of 0.34 cm/day (range 0.167–0.495 cm/day).

Using regression modelling, individual growth curves were derived for all children and were qualitatively similar, with distinct periods of continuous growth and periods of very slow or no growth (fig 2), in agreement with the distribution analysis. Saltations were not seen on regression modelling as the smoothing inherent in this technique masked abrupt changes of the magnitude determined by process control analysis. Using our definition of growth arrest (height increment less than or equal to 0.05 cm over seven or more days), an average of four stases was observed (range 0–8). Only two of the 46 children did not show periods of stasis greater than one week. The mean duration of stasis for the remaining 44 children was 18 days (range 8–52 days), accounting for an average 20% of the period of study. This value, however, is an underestimate of the true duration of stasis as the holiday periods prevent definitive identification of stases during these times. Growth velocity curves were also qualitatively similar for all children (an example is shown in fig 3), being described by a succession of growth spurts (mean 5, range 3–6) of mean duration 56 days (range 13–155 days) and mean interpeak interval of 69 days. Growth rates in the intervening periods were statistically indistinguishable from zero, corresponding to periods of stasis.

A composite velocity curve derived from all children showed a strong seasonal component to growth (fig 4), with a declining growth rate over the autumn months, reaching a nadir in January to March, followed by a marked growth spurt in the late spring and summer in accord with the findings of others.²²

Discussion

This study is a comprehensive evaluation of short term growth in mid-childhood. The

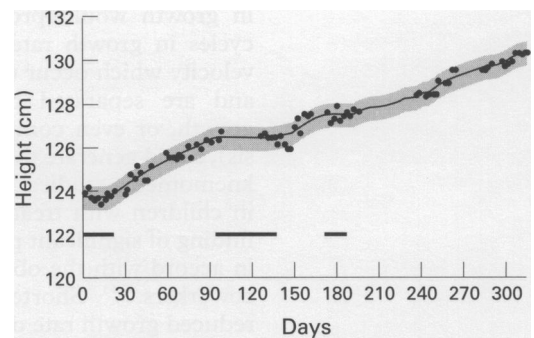


Figure 2 Growth curve for child A. Original measurements are indicated by closed circles. The bold line represents the estimated regression curve for height with the shaded area indicating simultaneous 95% confidence bands. Periods of growth arrest, defined as an increment in the smoothed heights of less than or equal to 0.05 cm over seven days, are indicated by the horizontal bars.

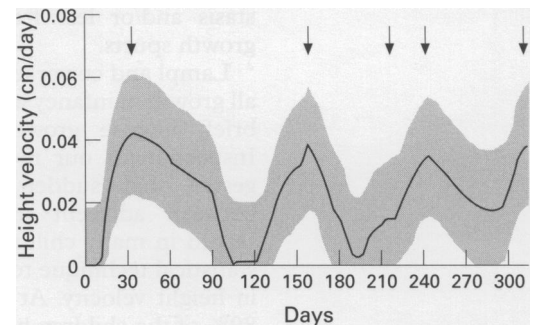


Figure 3 Growth velocity regression curve for child A. The estimated annualised growth velocity regression curve (bold line) and the simultaneous 95% confidence bands (shaded area) are shown. This child has five peaks of growth velocity (indicated by the vertical arrows; mean peak length 56 days, mean interpeak interval 69 days) with intervening nadirs when growth is statistically indistinguishable from zero.

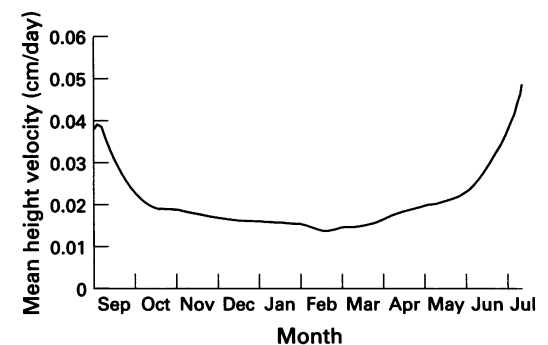


Figure 4 Mean growth velocity regression curve for all children. The x axis is graduated in months. The strong seasonal trend in growth is evident with declining growth rate in the autumn months, reaching a nadir in January to March, succeeded by the rapid spring growth spurt.

analysis of the growth data has been undertaken using a range of descriptive techniques and with no preconceptions about the nature of short term growth. It was recognised that measurement error, although minimised by the use of experienced observers, creates a significant problem for data interpretation; it was therefore taken into account in all analyses. By applying non-parametric techniques we have allowed the data to 'speak for itself', rather than attempting to prove or disprove a specific hypothesis. Nevertheless, this model of growth unifies many of the previous concepts of short term growth. For instance, the seasonal trend

in growth would produce significant annual cycles in growth rate.⁸ The peaks in growth velocity which occur on average every 69 days and are separated by nadirs of very slow growth, or even complete growth arrest (stasis), could generate the cycles of growth seen in knemometry studies¹⁰ and in catch-up growth in children with treated coeliac disease.⁶ The finding of significant periods of growth stasis is in accord with the observations of Lampl and coworkers.^{12,13} Shorter periods of markedly reduced growth rate or growth arrest have also been noted from knemometry studies of children treated with growth hormone experiencing intercurrent illness.²³ The physiological mechanisms that determine growth arrest are unknown. This has significant implications for the genesis of short stature, however, implying that this may arise from prolonged periods of stasis and/or less frequent and less intense growth spurts.

Lampl and coworkers^{12,13} have proposed that all growth in infancy and adolescence occurs in brief, intense growth spurts or saltations. Inspection of our raw height data also suggested that sudden increments in height between adjacent measurements were observed in many children. We therefore used a statistical technique to identify abrupt changes in height velocity. At a 1% significance level, 89% of the children had at least one change in velocity. It would be expected, however, that in a series of approximately 90 observations one significant velocity change could occur by chance. Further analysis using a 0.5% level (where one significant velocity change may be expected in 200 observations) revealed that 65% of children still had at least one 'saltatory' increment. This supports the concept that rapid changes in growth over intervals of a few days do occur. At least in mid-childhood, however, such a mechanism accounts for only a small amount of the total growth over one year.

The primary determinant of growth in normal healthy children with satisfactory nutrition is growth hormone and its secondary effector, insulin-like growth factor I. Longitudinal studies of the secretion and excretion of these hormones^{24,25} have shown wide variability over time. In particular, rhythms over days, weeks, and months in urinary growth hormone excretion, and by implication endogenous secretion, have been described.²⁵ It is therefore not surprising that growth is non-linear. The underlying pattern of growth that we describe does, however, infer that powerful coordinating influences regulate activity within the growth plates in a highly synchronised fashion. Growth hormone or insulin-like growth factor I would be a prime candidate for this regulatory role.

The highly variable structure of short term growth, with sustained growth spurts several weeks in duration and intervening growth stasis comprising 20% or more of the available time for growth, coupled with our knowledge of the complexity of growth hormone secretion, should also lead us to question the manner in which growth hormone is administered, particularly in states not deficient in

growth hormone, such as Turner's syndrome or idiopathic short stature. Intensification of growth hormone treatment in children deficient in growth hormone according to knemometry predictions of accelerating growth led to augmentation of the growth response, even though the total growth hormone administered over any given six month period was the same.²⁶ This is clear evidence that, even in growth hormone deficiency, varying the schedule of growth hormone administration can lead to better growth. It is certainly conceivable that for children not deficient in growth hormone periodic intensification of growth hormone treatment, possibly with intervening periods of no treatment, may lead to augmentation of the growth response. Thus a better understanding of short term growth and its underlying physiological mechanisms may also allow growth hormone to be used in a more appropriate and economical manner.

We conclude from the assessment of a large cohort of healthy prepubertal children that growth in mid-childhood is comprised of growth spurts, which last for a mean 56 days, with intervening periods of very slow growth or growth arrest. We also found that very short term changes in stature, characteristic of saltations, were found in most subjects, but would contribute only a small amount to the total growth over the year. This latter phenomenon may be a reflection of the fractal behaviour of growth described by Wales and Gibson² and could suggest the presence of chaotic dynamics within normal childhood growth. The physiological processes which give rise to this complexity remain to be discovered.

We thank the children who gave their time and effort, their parents and teachers; Sister Julie Jones for her technical expertise and assistance with measurements; Kaye Basford, University of Queensland, for generously providing her programme for analysis of mixtures of distributions; and Lilly Industries (UK) for financial support.

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