

## REVIEW ARTICLE

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**Catch-up growth: possible mechanisms**

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**Abstract** Many systemic diseases impair linear growth. If remission occurs, growth will often accelerate beyond the normal rate for age, a phenomenon termed “catch-up growth.” As a result, final height is improved, although this recovery of adult stature is frequently incomplete. Two principal models have been proposed to explain catch-up growth. The first model postulates a central nervous system mechanism that compares actual body size with an age-appropriate set-point and then adjusts growth rate accordingly. However, there is recent evidence that growth inhibition in a single growth plate is followed by local catch-up growth, a finding not readily explained by the neuroendocrine model. Thus, a new model has been proposed that places the mechanism within the growth plate itself. According to this model, growth-inhibiting conditions decrease proliferation of growth plate stem cells, thus conserving their proliferative potential. Additional research is needed to determine whether the mechanisms governing catch-up growth are local, systemic, or both.

**Key words** Catch-up growth · Growth plate · Glucocorticoids · Chondrocyte

**Introduction**

Optimal linear growth generally occurs only in the healthy, well-nourished individual. When the individual is malnourished or ill, growth is often down-regulated, presumably to conserve nutrients for vital functions. However, the growth deficit that accumulates during such periods can be partially recovered if the disease remits. Thus, the down-regulation of growth with illness repre-

sents, in part, simply a postponement until conditions improve.

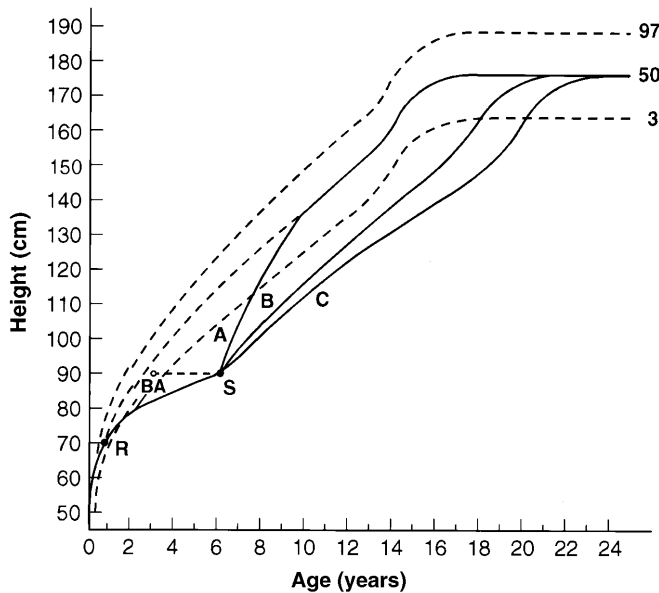
Generally, when growth-inhibiting conditions resolve, linear growth does not just normalize but actually exceeds the normal rate for age. This phenomenon, termed “catch-up growth,” occurs in humans and in other mammalian species. In humans, it has been described following a wide variety of growth-retarding illnesses, including Cushing syndrome [1], celiac disease [2], hypothyroidism [3, 4], anorexia nervosa/malnutrition, growth hormone deficiency, and intrauterine growth retardation [1].

Catch-up growth has also been described following treatment for a variety of renal disorders, such as primary distal tubular acidosis [5] and vesicoureteric reflux [6]. Catch-up growth is observed during remission of nephrotic syndrome and discontinuation of glucocorticoids [7, 8]. In children with chronic renal failure, the amount of catch-up growth following transplantation appears to depend on age and on the post-transplantation dose of glucocorticoid administered [9, 10, 11, 12].

**Patterns of catch-up growth**

Professor James Tanner has suggested that catch-up growth can occur in two different temporal patterns (Fig. 1) [13]. In the first pattern, the individual shows an early, marked growth acceleration that reduces the deficit rapidly, in humans, within a few years. The child then grows along this improved percentile until adult height is achieved (Fig. 1, curve A). In the second pattern, the child stays at a low percentile for years, growing at a normal velocity for either bone age (Fig. 1, curve B) or chronological age (Fig. 1, curve C). However, in this situation, bone maturation remains delayed so that growth continues beyond the usual age, leading to an improved adult height percentile. It is not clear whether these different patterns represent qualitatively distinct processes or simply demonstrate the spectrum of a single process. Often, catch-up growth appears to fall between these two

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**Fig. 1** Patterns of complete catch-up growth. Growth retardation occurs from *R* to *S*, with rehabilitation commencing at *S*. True, complete catch-up growth is represented by curve *A*. Complete catch-up growth due to delayed epiphyseal fusion is represented by curve *B* (average growth velocity for bone age) and curve *C* (average growth velocity for chronological age). *BA* bone age at start of rehabilitation [13]. Adapted with permission, Castlemead Publications

patterns, with some of the catch-up growth due to initial acceleration and some due to prolongation of growth. In growth hormone deficiency, for example, patients tend to follow an intermediate pattern [13].

In general, catch-up growth tends to be incomplete; the individual does not achieve the same adult height that would have been achieved had there been no growth impairment [3]. For a single patient, it is difficult to assess whether or not catch-up growth was complete. Even if the adult height falls within the normal range, the height that would have been attained in the absence of disease is unknown. However, in studies with a sufficient number of subjects, this issue can be addressed statistically. In these studies, some net loss of adult stature generally remains, particularly if the growth impairment was severe and long-standing [3, 7, 14]. It is possible that catch-up growth is never complete. Following mild, brief growth impairment, the final deficit may simply fall below the statistical detection limit of the study [15]. The amount of growth deficit remaining may also depend upon the nature of the growth impairment and the age at which it occurs [16].

### The “sizostat” theory

In 1963, Professor Tanner published an ingenious model to explain catch-up growth. He proposed that a mechanism might exist, probably within the brain, which compares the actual body size with an age-appropriate set-

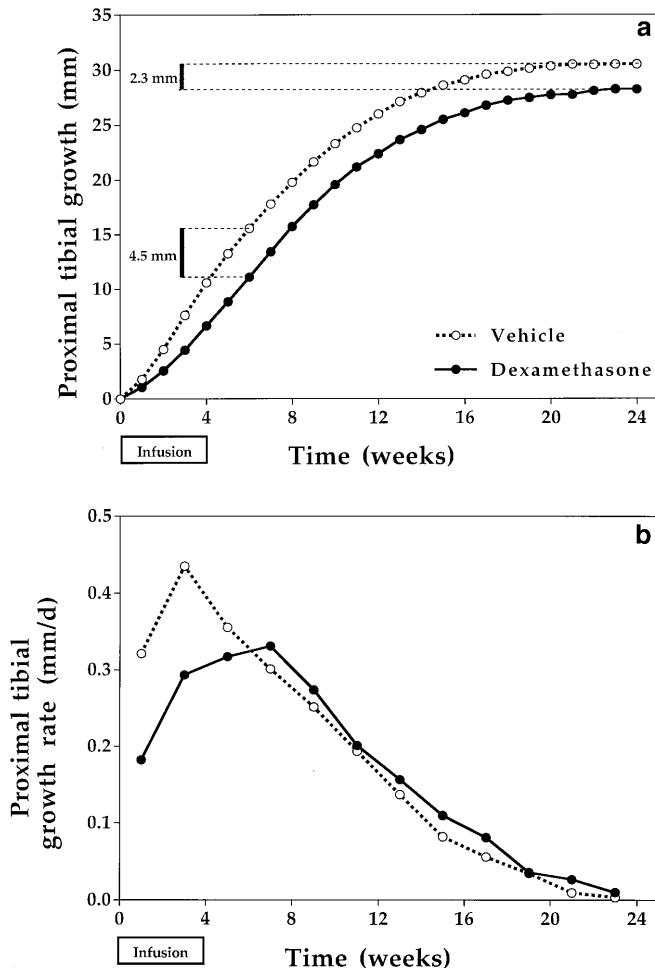
point and then adjusts the growth rate accordingly. The age-appropriate set-point might be based on the concentration of a substance within nerve cells that increases with age. The assessment of actual body size might be based on the concentration of a circulating substance that increases as the animal grows. Based on these assessments, the central nervous system “sizostat” mechanism would adjust the growth rate to decrease the discrepancy between the actual size and the age-appropriate set-point. This growth rate regulation might be achieved by altering production of efferent systemic growth-regulating signal(s), possibly some combination of pituitary hormones [17].

According to Tanner’s model, growth inhibition would lead to an increasing discrepancy between the actual size and the age-appropriate set-point. The sizostat mechanism would sense this disparity and alter production of the efferent growth-regulating factors, thus initiating catch-up growth. As the discrepancy diminished, the mechanism would decelerate growth, such that the height would not overshoot but rather ease into an improved height percentile. In his writings, Professor Tanner commented that his model was simply theoretical and that the mechanism may be local rather than systemic.

Some evidence has been cited in favor of a central set-point for body size [18]. In newborn mice, irradiation of the head causes growth stunting. Such animals are capable of catch-up growth after fasting, but only to the stunted body size. Based on these findings, it has been suggested that head irradiation resets the set-point for body size. However, the data are also compatible with a simple alternative explanation [19, 20]. Catch-up growth only occurs when growth-inhibiting conditions resolve. Irradiation leads to irreversible damage to nervous and pituitary tissue and thus may not satisfy this basic requirement for catch-up growth.

### Mechanisms intrinsic to the growth plate

We have proposed an alternative hypothesis, that the mechanism governing catch-up growth resides not in the central nervous system but rather in the growth plate [19]. To test this hypothesis, we asked whether transient suppression of growth within a single growth plate would lead to local catch-up growth. Using an osmotic minipump, we administered dexamethasone directly into the proximal tibial growth plate of 6-week-old rabbits and vehicle into the contralateral growth plate. Dexamethasone slowed proximal tibial growth during the 4-week infusion compared with the contralateral vehicle-treated control (Fig. 2). After the infusion ended, the growth rate of the dexamethasone-treated side not only normalized but actually surpassed that of the control side (Fig. 2b), thus correcting approximately half of the growth deficit (Fig. 2a). This catch-up growth was observed solely in the growth plate in which the growth inhibition had occurred; growth in the distal tibia and in the femur was unaffected.



**Fig. 2** **a** Cumulative proximal tibial growth during and after local dexamethasone infusion into the proximal tibial growth plate of 6-week-old rabbits. Closed symbols represent the mean cumulative growth of dexamethasone-treated proximal tibiae. Open symbols represent the mean cumulative growth of the vehicle-treated proximal tibiae. The box below the X-axis represents the infusion period. The vertical bars at 6 and 24 weeks represent the difference in the cumulative growth between the dexamethasone- and vehicle-treated sides [19]. Reproduced with permission, The Endocrine Society. **b** Growth rates of dexamethasone- and vehicle-treated proximal tibiae. The growth rate was calculated from the proximal tibial growth over 2-week intervals [19]

Because the catch-up growth occurred in a single growth plate, it could not be explained by the Tanner model. A neuroendocrine mechanism, or any systemic mechanism that involved circulating factors, would have affected all growth plates and thus could not by itself account for the observed anatomical specificity. Therefore, the data suggest that the underlying mechanism is intrinsic to the growth plate.

To explain our findings, we proposed that catch-up growth arises from a delay in the normal senescence of the growth plate [19]. Normally, the rate of longitudinal bone growth (and hence linear growth of the animal) falls progressively with age [21, 22]. Kemper and Walker [23] showed that this senescent decline in growth rate is due, in part, to a decrease in the rate of growth plate

chondrocyte proliferation. We hypothesized that this proliferative rate diminishes with each successive stem cell cycle, and thus growth plate senescence is a function not of time per se but rather of the cumulative number of divisions the stem cells have undergone.

Glucocorticoid slows linear growth by suppressing proliferation of growth plate chondrocytes [23]. Therefore, at the end of the infusion, the dexamethasone-treated stem cells may have undergone fewer cell divisions than the vehicle-treated stem cells. According to our hypothesis, the dexamethasone-treated cells were thus less senescent, and, consequently, proliferated more rapidly than the vehicle-treated cells, leading to catch-up growth.

Our model is consistent with a concept proposed in 1914 by Osborne and Mendel [24]. They showed that prolonged nutritional deprivation in the rat was followed by growth at an age well beyond the normal growth period. They concluded that, "... it by no means follows that the familiar cessation of growth is due solely to a loss of a capacity to grow incidental to age ... the capacity to grow is only lost by the exercise of this fundamental property of animal organisms"[24].

## Conclusion

In summary, catch-up growth occurs after a wide variety of growth-inhibiting conditions. It tends to be incomplete, and therefore, the child may not achieve his genetic height potential. Recent evidence suggests that catch-up growth is determined, at least in part, by a mechanism intrinsic to the growth plate. Further elucidation of the responsible mechanisms may suggest strategies to optimize linear growth in children with chronic diseases.

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