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 represents, 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
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 by achieved by altering production of effegent 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 effegent 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.