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Catch-up Growth

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I. Introduction

AS EARLY as the beginning of this century, it was reported that animals with retarded growth due to undernutrition can achieve a growth rate higher than normal for chronological age after removal of the food restriction (1–3). A supranormal height velocity may also be observed in children recovering from starvation or illness. In medical literature, little or no attention was paid to this phenomenon of accelerated linear growth until the second half of the 20th century. One of the first reports on this subject was published in 1963 (4). In that article, Prader *et al*. (4) introduced the term *catch-up growth* to describe the phase of rapid linear growth that allowed the child to accelerate toward and, in favorable circumstances, resume his/her pre-illness growth curve.

Today, more than 30 yr have passed since the publication of Prader's classic paper, and various investigators have tried to reveal the physiological basis of catch-up growth. Despite all efforts, the mechanisms responsible for this striking human capacity have not yet been fully clarified. Therefore, a continuation of research in this field is needed, and an update of the current knowledge seems worthwhile.

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II. Catch-up Growth: Theoretical Considerations

A. Definition

Catch-up growth may be defined as a height velocity above the statistical limits of normality for age and/or maturity during a defined period of time, following a transient period of growth inhibition. The effect of catch-up growth is to take the child toward, or in favorable circumstances, right onto his/her original preretardation growth curve (5, 6). Figure 1 presents a graphical representation of catch-up growth.

B. Catch-up growth vs. compensatory growth

Although *catch-up growth* and *compensatory growth* appear to be synonymous, a distinction between these terms is jus-

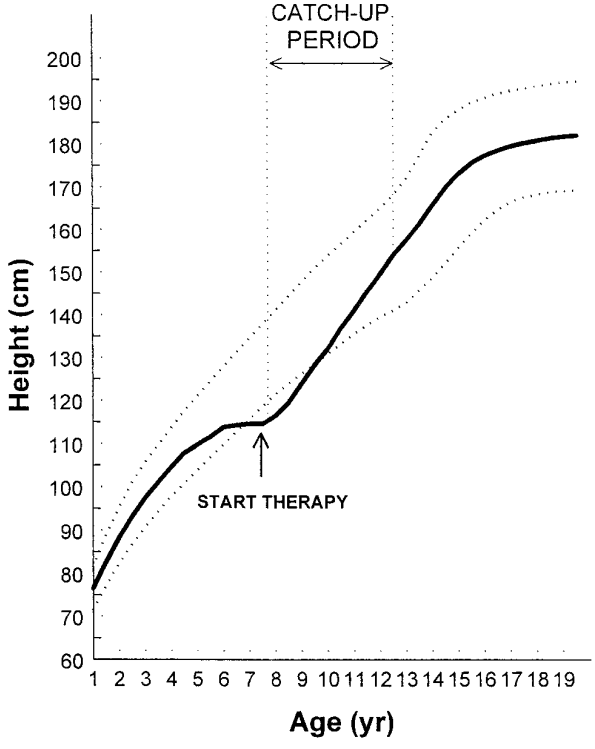

FIG. 1. Catch-up growth.

tified. In contrast to catch-up growth, compensatory growth is used not only to address growth of the whole organism, but also to describe overgrowth of a single organ, or part of an organ, when another part is removed. Good examples of compensatory growth are the hypertrophy of the remaining kidney after its contralateral partner has been removed, or the regeneration of liver tissue after partial hepatectomy. In this sense, compensatory growth has been defined as the effort of an organ to overcome the effect of some functional inadequacy forced upon the body as a whole, by deploying to greater effect the organ's existing cells, by cell enlargement, cell division, or both (7). The latter is consistent with the distinction Williams (6) made between catch-up and compensatory growth. Williams stated that compensatory growth is used to describe the type of growth that occurs after the loss of an *actual* mass of tissue and may be viewed as being controlled by a simple feedback mechanism working on physical mass or physiological load, whereas catch-up growth is rapid growth that compensates for the loss of *potential* tissue and thus cannot be accounted for by a simple feedback mechanism. The mechanism responsible for catch-up growth must anticipate a future lack of tissue, while the mechanism underlying compensatory growth reacts to a present loss of tissue. In a more abstract manner, compensatory growth depends on an alteration in spatial parameters, and catch-up growth is a response to an alteration in a temporal parameter.

C. Canalization

In the long term, human growth is a fairly regular process, characterized by a pattern of changing height velocity from infancy to adulthood. A high velocity from birth with a rapid deceleration up to about 3 yr of age is seen, followed by a period with a lower and slowly decelerating velocity up to puberty. Puberty starts with an increased velocity and after the age of peak velocity a deceleration is observed until growth ceases (see Fig. 2).

In the short term, however, the height velocity of a healthy individual is much more variable. In addition to spontaneous height velocity fluctuations with seasonal (8) or longer periodicity (9), short-term velocity variations have been demonstrated (10–12). Therefore, the line in Fig. 2 is probably a smoothed version of the true velocity curve, which would look much more irregular.

Taking into account its regularity in the long term, linear growth must be under the control of a dynamic and complex system that makes the growing child return to its path of growth after deviation. This tendency to keep to a narrow and predictable track of growth has been called "canalization"(13) and is a prerequisite for catch-up growth. If normal linear growth was not canalized, it would not be possible to identify a period of catch-up growth. In clinical terms, canalization means that the individual growth curve parallels the centile curves of growth charts.

In the prepubertal period canalization is clearly recognizable, but thereafter its presence becomes less pronounced, and a crossing of the centile curves is frequently seen. This is caused by the large interindividual variation in age at onset of puberty, the rate of progression through puberty, and, to a lesser extent, the magnitude of the pubertal growth spurt. For this reason, a catch-up growth spurt is easily recognizable in the prepubertal period, but thereafter it is often impossible to discriminate between the pubertal growth spurt and a catch-up growth acceleration.

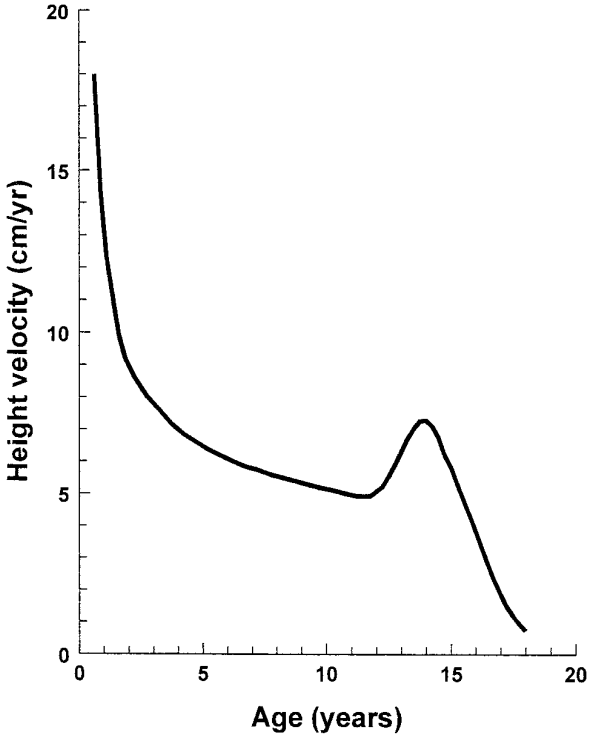

FIG. 2. Height velocity for chronological age.

Within one individual, the degree of canalization varies among the various growth parameters. Head circumference, height, and skeletal maturation tend to parallel the centiles more closely than weight and skinfold thickness.

D. Catch-up growth vs. resumption of a normal height velocity

Once the growth-suppressing problem has been resolved, one would expect height velocity to normalize. However, although the resumption of a normal height velocity may already be considered as a favorable, or even the maximal, result of therapy, if the child simply returns to and then maintains a normal height velocity, catch-up growth does not occur. Catch-up growth is characterized by an increase of percentile position and thus requires that height velocity exceeds the statistical limits of normality for age and/or maturity at some point.

E. Types of catch-up growth

It has been suggested that three different types of catch-up growth can be distinguished (14, 15). In type A, when growth restriction ceases, height velocity increases to such an extent that the height deficit is swiftly eliminated. The height velocity may increase up to 4 times the mean velocity for chronological age. Once the original curve is reapproached, height velocity returns to normal. Type A catch-up growth

is seen as the classic example of catch-up growth and is common in infancy and childhood. Such a pattern of catch-up growth may, for example, be observed after institution of a gluten-free diet in childhood celiac disease. In type B, when growth restriction ceases, a delay in growth and somatic development persists. However, growth continues for longer than usual, so that ultimately the growth arrest is compensated. This type of catch-up growth has only a small or no increase of height velocity compared with the mean velocity for chronological age. As it occurs during adolescence, it is often impossible to distinguish a catch-up spurt in this period from the pubertal growth acceleration. It may be seen, for example, in children with a constitutional delay of growth. Two excellent examples of type B catch-up growth were given in a report on two hypopituitary males, in whom human GH (hGH) treatment was started only at the age of 24.3 and 22.7 yr, with androgens added at 26.0 and 24.9 yr (16). These subjects had gained 21 and 22 cm in height at age 29.1 and 27.9 yr at the time when hGH was stopped. Type C is a mixture of types A and B. When growth restriction ceases, there is an increase in height velocity as well as a delay and prolongation of growth. Although this subdivision of catch-up growth in different types appears reasonable, the borderlines between types A, B, and C are not sharply delineated and in practice a distinction cannot always be made, indicating that the practical importance of this classification should not be overestimated.

F. Assessment of duration and success of catch-up growth

The increase of height velocity, characteristic for catch-up growth, usually becomes clearly recognizable in the first year after removal of the growth restriction. At that time, the length of the total catch-up period and the ultimate success of catch-up growth are hardly predictable. Actually, these two factors can only be evaluated retrospectively, when final height has been reached. The ultimate success of catch-up growth is difficult to predict at an early stage because an exact prediction of final height in a child who still has several years left to grow is hardly possible. One of the most important factors rendering such a prediction unreliable is the large variability in onset, duration, and magnitude of the pubertal growth spurt.

If catch-up growth coincides with the pubertal growth spurt, final height may be compromised, possibly due to a too-rapid bone maturation (17, 18). If, in contrast, the onset of puberty is relatively late, bone maturation progresses slowly for a long period, allowing the child to achieve an actual final height well above initially expected final height.

III. Secondary Growth Disorders and Subsequent Catch-up Growth

The hallmark of secondary growth disorders is that the failure of growth is the result of a primary defect located outside the osseous and supportive tissues. Examples of primary defects that may lead to secondary growth failure are malnutrition, endocrine disorders, disorders in specific organ systems, etc.

In general, the principal aim of therapy in secondary growth disorders is to provide adequate treatment for the primary defect. If this succeeds, the growth-inhibiting conditions resolve; the growth retarding factor is removed (*e.g*, treatment of a chronic infection) or the deficient factor is substituted (*e.g*., T_4, GH). As soon as the essential requirements for normal growth are being fulfilled, a spontaneous acceleration of linear growth usually ensues which, if resulting in an increase of percentile position, can be considered as catch-up growth.

Thus, secondary growth disorders provide interesting human models by which to study catch-up growth *in vivo*. It is especially important to derive as much knowledge as possible from observations of catch-up growth in these disorders because well designed studies on human catch-up growth are difficult to realize for two, mainly ethical, reasons. First, the investigator cannot deliberately produce a growth disorder in a child. Second, children recovering from a secondary growth disorder usually do not benefit from invasive or otherwise unpleasant techniques, applied in search for the fundamental mechanisms governing catch-up growth.

In the following sections we will briefly describe the early studies on catch-up growth, followed by the findings on catch-up growth in a number of secondary growth disorders. Although direct extrapolation of results from animal experiments to the human situation is not possible because there are considerable differences in growth and growth regulation between humans and animals, data from animal studies are also presented.

A. The early studies

In 1954 Bauer (19), while working with Dr. Prader in Zürich, published one of the first papers in pediatric literature on catch-up growth. He described the growth pattern of 34 children with nephrotic syndrome. Before the onset of the disease, height velocity was normal. During the disease growth was progressively retarded, but after recovery the growth retardation was compensated by a phase of accelerated growth. Bauer noticed that this "Aufholphase" lasted approximately twice as long as the period of illness.

A few years later, Prader *et al.* (4) provided a broader insight in the subject of human catch-up growth by giving a number of examples of catch-up growth in children with disorders such as anorexia nervosa, renal disease, Cushing's syndrome, celiac disease, and hypothyroidism. Despite the diversity of disorders, these children all showed a slowing down of statural growth during the active phase of the disease, and a period during which their growth rate was above the usual rate for age after the onset of therapy. During the recovery period some children reached a height velocity up to 4 times the average rate for chronological age and 3 times the average rate for skeletal age.

B. Malnutrition

1. Human studies. On a worldwide basis the most frequent cause of being small at birth and short in infancy and childhood is protein-energy malnutrition. Most studies on growth in malnourished children have focused on weight. However, a few studies have also documented catch-up growth in

height after malnutrition, either in the immediate recovery period or in the long term.

In the immediate recovery phase during hospitalization, none (20) or only a subgroup (21) of severely malnourished children showed signs of catch-up growth in height. The subgroup who already began to catch-up during hospitalization did not differ in age or sex from the total sample but contained a greater proportion of nonedematous children. Children in this subgroup were also more stunted initially than the group as a whole. Moreover, in most children, linear growth started only after they had attained at least 85% weight for length (21). The latter was also observed in children with short stature due to self-imposed restriction of food intake arising from a fear of becoming obese (22). These children also showed an acceleration of linear growth only after weight gain had been established for 1 to 3 months.

Studies on the long-term height prognosis after an episode of severe malnutrition have produced conflicting results. While complete recovery to a normal adult height was reported in some early studies (23, 24), others have suggested that severe malnutrition results in a permanent height deficit (25–28). The discrepancy between the outcome of these studies may be attributed to factors such as the control group with which previously malnourished children were compared, the degree of inadequacy of the home environment to which the children returned after discharge from hospital, and the more general problem that follow-up studies in human subjects cannot be conducted under fully controlled experimental conditions, thereby making isolation of malnutrition as an independent variable practically impossible.

Recently, Golden (29) attempted to determine whether complete catch-up is possible for stunted malnourished children. He worded the uncertainty about the final outcome of catch-up growth after malnutrition by stating that "*the available data could be interpreted to show that a period of malnutrition in the first 2–3 yr irrevocably changes the child so that he is 'locked into' a lower growth trajectory with a lower potential for future growth. The alternative hypothesis is that full catch-up growth is possible. However, this is not observed in practice because the correct conditions are not satisfied because in most populations environment and diet do not change*." His assumption that full catch-up growth is theoretically possible is supported by observations that the retardation of bone maturation is not significantly different from the height retardation (25, 27).

2. Animal experiments. One of the first references to the effects of undernutrition on growth in animals dates back to 1908. Waters (1) showed that previously undernourished beef steers could recover and reach a normal mature weight and height. Since then, many animal studies, especially in rats, have been performed.

After mild nutritional restriction, mammals and birds generally achieve their normal body size and conformation at a later stage of growth (30). Periods of prolonged or excessive restriction may, however, cause permanent stunting. Wilson *et al.* (30) have identified six factors that appear to be important for the extent of compensatory growth:

1. The nature of undernutrition; very severe protein restriction may have a more harmful effect than very severe energy restriction.

2. The severity of undernutrition; the more severe the restriction, the greater is the initial rate of gain immediately after realimentation, but the smaller is the ultimate weight.

3. The duration of the period of undernutrition; excessively long periods of restriction may result in permanent stunting.

4. The stage of development of the body at the start of undernutrition; it was suggested that undernutrition in the earlier stages of growth has a more harmful effect for an animal than restriction at a later stage, and that the ability to recover and to reach normal mature size is consequently reduced.

5. The relative rate at which the species matures; slower maturing realimentated animals make a more rapid recovery from undernutrition than faster maturing ones.

6. The pattern of realimentation; the higher the plane of nutrition upon realimentation, the more rapid and the greater the recovery in weight of cattle.

In rats, undernutrition during the entire suckling period was followed by complete or almost complete catch-up growth in body length in both sexes (5, 31). Catch-up growth in weight was complete in female rats (31), but not in male rats (5). The permanent weight deficit in males was attributed to a deficit in soft tissue and not to a skeletal deficit (5). In a later experiment, where undernutrition was imposed for varying time periods during the suckling period, it was shown that the permanent weight deficit in male rats probably developed between day 8 and day 15 of the suckling phase, indicating that this might be a period of maximum sensitivity. Rats fasted for 1–3 days after weaning showed almost complete catch-up growth in body weight and tail length (32). Undernutrition imposed on rats at different ages, so that the growth retardation was produced either during the suckling period, during the period of peak body weight growth, or even thereafter, was followed by complete catch-up growth in length in all groups (33). Altogether, these experiments show that, in rats, food restriction is almost invariably followed by complete catch-up growth.

Widdowson and McCance (34) have suggested that the completeness of catch-up growth after malnutrition is largely dependent on the time of onset of the retardation. The earlier in life the undernutrition is imposed, the more serious and permanent its effects would be (35). Although the biological basis for failure of catch-up growth after early food restriction was not entirely clear, the timing of the restriction in relation to two consecutive phases of normal tissue development was considered to be crucial. According to the theory of Winick and co-workers (36, 37), all organs and tissues grow first by multiplying their cells and subsequently by increasing the size of those cells. Reduction in cell numbers, due to food restriction at an early stage of life, would result in permanent stunting, whereas reduction in cell size, caused by food restriction at a later age, would be fully recoverable.

More recently, the concept of such a critical period in development has been challenged. In growing liver, kidney, heart, and gastrocnemius muscle, Sands *et al.* (38) found that cell size increases much earlier than previously suggested, and that cell multiplication in the same organs and tissues continues unabated until growth comes to an end. This suggests that the earlier reported, circumscribed phase of cell

division, thought to be particularly vulnerable to permanent stunting, may not exist. Although it is thus not fully clear whether a critical period in development of rat tissues truly exists, one should nevertheless be very careful with the extrapolation of these rat data to the human situation especially because a rat is born at a much earlier stage of development than a child (35).

C. Celiac disease

Celiac disease causes malabsorption and growth retardation in infancy and childhood. In a large number of children with celiac disease, failure of linear growth is a dominant symptom (39, 40), especially when diagnosed beyond toddler age (41, 42). In some patients, short stature is even the only symptom of celiac disease (40, 43–46).

Celiac disease provides a human model for investigation of catch-up growth after malnutrition as it occurs, in contrast to malnutrition in third world countries, under fully controlled circumstances. Children with celiac disease are usually not exposed to intrauterine or early infantile malnutrition and they have suffered from a well defined period of malnutrition caused by a specific disease process that can be adequately treated. Moreover, the entire course of their illness and subsequent rehabilitation usually takes place in satisfactory environmental conditions.

Gluten withdrawal is an effective treatment for growth failure in celiac disease. After institution of a gluten-free diet, most patients show a recovery of weight within 6–12 months, whereas height tends to normalize within approximately 2–3 yr (47–49). Thus, in line with the findings in malnourished children (21), weight catches up more quickly than height.

Although a few observations suggest that the chances to achieve full catch-up growth are reduced by a higher age at diagnosis (42, 50) or insufficient compliance to the gluten-free regimen (51), the available data generally indicate that celiac disease does not influence final height (43, 52, 53). Subjects with gastrointestinal symptoms, in whom treatment had been initiated before adulthood, reached a mean height similar to the normal population, while subjects with no gastrointestinal symptoms during childhood reached a normal final height even without treatment (52, 53).

D. GH deficiency

1. Human studies. In theory, catch-up growth after GH deficiency can be studied either after a normal pituitary GH secretion has temporarily been blocked or after a reduced pituitary GH secretion has been fully corrected. In practice, however, temporarily blocking GH secretion in healthy children is unacceptable for ethical reasons, and fully correcting a reduced pituitary GH secretion is impossible because GH replacement therapy is not physiological as it lacks normal GH pulsatility and bears the risk of under- or overreplacement. Consequently, in man, the optimal model for the study of catch-up growth after GH deficiency is not available. Therefore, data from comparable conditions must be exploited to their maximum.

One of the few conditions in man in which a reversible insufficiency of GH secretion has been demonstrated is psychosocial short stature (54). In 1967 Powell *et al.* (55) described a number of children with failure of linear growth without organic background in association with behavioral disturbances and psychosocial stress. This type of growth failure has been termed psychosocial short stature and is considered to be a syndrome with many variables (56). When these children are placed in a nurturing environment, catch-up growth may occur spontaneously (57), but ceases again when they are returned to the original circumstances (58).

A proportion of children with psychosocial short stature have GH insufficiency (59). When GH insufficiency is present, reversibility can usually be demonstrated when the adverse environment is changed (54, 59–61). Normalization of GH secretion has not only been shown by analysis of GH responses to pharmacological stimuli (59, 60), but also by analysis of repeated physiological GH secretion profiles (54, 61). In the latter studies, the recovery of normal GH secretion was characterized by an increase in amplitude of GH peaks without a significant change in GH-secretory periodicity (54, 61).

Recently, it has been suggested that, within the total group of children with psychosocial short stature, a special subgroup of children with so-called "hyperphagic short stature" can be identified. These children are clinically recognizable by means of behavioral and developmental criteria, among which hyperphagia and reversible GH insufficiency constitute essential symptoms (62).

Another important condition in which catch-up growth after GH deficiency can be studied is in children with GH deficiency during GH replacement therapy. Since GH was introduced for the treatment of children with GH deficiency in 1958 (63), several aspects of GH therapy, *i.e.*, production method of GH, administration route, and injection frequency, have been modified. Although it has been reported that these modifications have led to larger increases of height velocity in the short term (64, 65), data on final height after GH replacement therapy given according to the newer treatment regimens are still limited.

Consequently, most of the long-term results of GH treatment have been obtained from patients treated according to the older methods. These results demonstrate that, although GH treatment induces a significant increase of height velocity during the first years of therapy, the average height after several years of therapy, as well as final height, remains approximately 2–3 SDS below the population's mean (66–72). Major determinants of final height, *i.e.*, ultimate success of catch-up growth, after GH therapy are height at start of therapy (71–73), height at onset of puberty (71, 72, 74, 75), and target height SD score (71, 73). Early diagnosis and treatment are thus of paramount importance in the treatment of GH deficiency. Preliminary studies have indicated that final height comes close to target height on the newer treatment regimens (76).

2. Animal experiments. The recently described GH-deficient mutant dwarf rat has offered investigators a new and useful laboratory model of GH deficiency (77). In contrast to the surgically prepared hypophysectomized rats that have a lack of all pituitary hormones, this rat has a selective deficiency

for GH and, in contrast to mouse models, its size lends it to physiological experiments involving chronic cannulation and blood sampling. If these GH-deficient rats are left untreated, they continue to grow but at a rate 40–50% less than that of their healthy controls (77). Their growth rate can be restored by injections or infusions of GH and, to a lesser extent, by infusions with insulin-like growth factor (IGF) (77, 78). The results of a recent study on the effect of gonadectomy on growth and GH responsiveness in the GH-deficient dwarf rats (79) have confirmed previous observations in hypophysectomized rats (80, 81) that intravenous pulsatile GH treatment is more effective in stimulating body weight gain and tibial bone growth than a continuous GH infusion. In addition, they have shown that this is also true for increasing length in the rat. Moreover, this study demonstrated that the responsiveness to pulsatile GH treatment was not affected by the removal of gonadal steroids, at least in the short term (79).

E. Hypothyroidism

1. Human studies. Hypothyroidism in childhood is almost invariably associated with growth failure. This failure of growth is probably caused by a decrease of the direct effects of thyroid hormones on skeletal growth and by a secondary reduction in GH secretion and concentration of IGF (82–84). After the onset of T_4 replacement therapy, these abnormalities usually resolve and a period of catch-up growth ensues.

In the past, it has been suggested that catch-up growth in children treated for congenital or juvenile hypothyroidism is complete, and that such children usually reach their expected adult height (85, 86). This view is in line with studies describing growth in children in whom treatment has been started at a young age (87, 88), but it is not supported by recent reports showing a failure of catch-up growth in children in whom treatment has been initiated after a long period of untreated hypothyroidism (17, 18, 89). Three possible explanations for the observed failure of catch-up growth have been proposed: 1) overtreatment with T_4, 2) reduced potential for catch-up growth induced by hypothyroidism, and 3) puberty's limiting effects on the residual growth period.

2. Animal experiments. In male rats, Mosier and co-workers (32, 90) observed incomplete catch-up growth in body weight and tail length, one of the indices of skeletal growth in the rat, if hypothyroidism was induced in the postweaning period by feeding them a diet containing propylthiouracil for 17 to 20 days.

In newborn rats of both sexes, Meisami (91) induced hypothyroidism by treating them from birth with the antithyroid goitrogen *n*-propylthiouracil, given in the drinking water. One group received this treatment until the age of 25 days (weaning age), another group until the age of 50 days (age of sexual maturation), and a third group until the age of 120 days. After 120 days of hypothyroidism, the mortality percentage was 75% in the third group, and therefore this was considered to be an extreme limit for prolongation of hypothyroid retardation. The male rats generally showed higher catch-up growth rates of weight and reached significantly higher body weights compared with the females. However, when growth recovery was followed for up to 6 months, it was found that the male rats had failed to attain complete catch-up growth in weight, regardless of the age at which propylthiouracil administration had been stopped, while the females of all age groups were able to achieve this goal. No systematic analysis of body length was undertaken in this study, but one set of measurements in 100-day-old females rehabilitated from day 25 revealed no difference in tail length compared with normal controls. In male rats, however, tail length was significantly shorter than that of normal controls.

In contrast with Mosier *et al.*, Meisami concluded that in the female rat complete catch-up growth of weight is possible, even after an extremely long period of hypothyroidism. The discrepancy between the sexes was explained by a difference in catch-up capacity; whereas Mosier *et al.* used only male rats, Meisami used rats of both sexes. Meisami argued that this difference in catch-up capacity, which is in agreement with the findings in malnourished rats (5, 31) (see *Section III.B*), could be due to sexual differences in responsivity to GH or androgens.

F. Corticosteroid excess

1. Human studies. Prolonged exposure to corticosteroid excess, whether of exogenous or endogenous origin, leads to significant impairment of linear growth in childhood (92). The capacity of exogenously administered corticosteroids to suppress linear growth appears to depend largely on dosage and duration of corticosteroid therapy and the frequency with which corticosteroids are administered (92). Although the growth-inhibiting effect of corticosteroids has long been recognized, the mechanism that causes the growth failure of linear growth is not fully clear. Corticosteroids probably exert both direct, local effects on the epiphyseal growth plate chondrocytes (93, 94) as well as indirect, systemic effects (95).

Once the exposure to corticosteroid excess has ceased, catch-up growth may be observed. The efficacy of catch-up growth is difficult to assess for two reasons: first, because it is often impossible to distinguish between irreversible damage caused by the preceding corticosteroid exposure and the natural course of the underlying disease; and second, because there are few data on final height of children who have only temporarily been exposed to corticosteroid excess and subsequently have had enough time to perform a catch-up spurt before closure of the epiphyses.

In man, adequately treated Cushing's syndrome is one of the few conditions allowing an assessment of catch-up growth after *transient* exposure to corticosteroid excess. Prader *et al.* (4) reported on successful catch-up growth in a girl with Cushing's syndrome after removal of the adrenal tumor. However, Mosier *et al.* documented failure of catch-up growth in a similar case (96). In a recent study, final height was compromised in all patients who had suffered from endogenous Cushing's syndrome during childhood or adolescence (97). However, these data should be interpreted cautiously as endogenous Cushing's syndrome is not a pure model for glucocorticoid excess; before treatment there is often, depending on its cause, a concomitant excess of adrenal androgen and estrogen, whereas after surgical treatment of Cushing's disease subtle GH deficiency or hypothyroidism may influence statural growth.

More data are available on long-term growth in children who have been exposed to *long-lasting* corticosteroid excess. In 20 prepubertal children with nephrotic syndrome, 1–4 yr of alternate-day prednisone treatment in dosages ranging from 0.5–2.0 mg/kg did not affect statural growth negatively: in only 1 of 20 children, a height loss of 0.5 SD occurred (98). In a group of 80 children with a history of steroid-responsive nephrotic syndrome who had received a mean total prednisolone dose of 15 g/m^2 with a median duration of therapy of 1.9 yr, height SD score 5–24 yr after diagnosis was −0.3 SD. The subgroup of postpubertal patients who had completed growth had a mean height SD score of −0.2, equivalent to a height on the 40th centile and not significantly less than that of the normal population (99). A meta-analysis, in which statistical integration of the results of 21 studies including 810 asthmatic children on the effect of oral and inhaled corticosteroids on growth was performed, revealed a significant but small tendency for corticosteroid therapy in general to be associated with diminished final height (100). However, this effect varied for oral and inhaled drugs; significant weak growth impairment was observed for prednisone and "other oral corticosteroids," whereas a significant moderate tendency to obtain normal stature was observed for inhaled beclomethasone dipropionate. There was no statistical evidence for beclomethasone dipropionate therapy to be associated with growth impairment at higher doses, for longer therapy durations, or among patients with more severe asthma (100).

2. Animal experiments. Treatment of two groups of rats, 37 and 38 days of age, with daily subcutaneous injections of 5 mg cortisone over a period of 4 or 8 days resulted in permanent stunting of body size (32). The absence of catch-up growth in the recovery period was thought to result from cortisone-induced alterations in chondrocyte morphology (32) and abnormal energy use (101). Rats stunted by high-dose cortisone treatment were able to catch-up after a 48-h period of fasting, but only to the body size of nonfasted, cortisone-treated controls (102). In prepubertal monkeys, height velocity, as measured by lower leg length growth, decreased during dexamethasone injections and increased after cessation of corticosteroid administration (103). Although this indicates short-term catch-up growth, the final outcome was not reported.

These results suggest that the capability to catch-up growth is not fully destroyed, but probably at least partially reduced, by corticosteroid treatment.

G. Intrauterine growth retardation (IUGR)

Infants born with IUGR constitute a heterogeneous group. This heterogeneity results from the lack of a generally accepted standard definition of IUGR (104) and the large variability in the underlying causes of retarded growth. IUGR may be secondary to a chromosomal abnormality, an intrauterine infection, a maternal disease, placental dysfunction, or maternal cigarette smoking. However, in the majority of patients with IUGR, the cause remains unknown.

Although most children with IUGR show spontaneous catch-up growth during the first 2 yr of life, approximately 15% to 40% of the children with IUGR do not achieve complete catch-up growth (105–111). Despite the wide variability of this percentage, it is thus generally known that IUGR is a common cause of persisting short stature (112).

In seeking the cause of insufficient catch-up growth, it has been demonstrated that 25–60% of children with short stature related to IUGR have a subnormal GH secretion (113–116). Studies aimed at improvement of linear growth by administration of exogenous GH in children with IUGR have provided evidence that in some of these children GH replacement therapy leads to satisfactory short-term results, but the effect on final height remains to be determined (113, 115, 117–121).

IV. Mechanisms Regulating Catch-up Growth

Although Prader *et al.* (4) provided an excellent description of catch-up growth in 1963, these workers had to conclude that the biological mechanism controlling this phenomenon was still unknown. Shortly afterward, Tanner (122) discussed this issue and developed a hypothesis as to how catch-up growth might be regulated.

A. The neuroendocrine hypothesis

Tanner's hypothesis, also called the *neuroendocrine* hypothesis, involves a mechanism that is able 1) to recognize the degree of mismatch between the size the organism ought to have (the target size) and the size it actually has, and consequently 2) to adjust growth rate according to the degree of mismatch.

The target size is represented by the steadily increasing concentration (or organization) of something somewhere, most likely in the brain, which Tanner called the "time tally." The actual body size is represented by a circulating inhibitor factor produced by growing tissues and present in a concentration reflecting the size of the organism. This inhibitor factor acts as a kind of feedback signal that satisfies in some way the receptors of the time tally. The amount of unsatisfied receptors is proportional to the degree of mismatch and, perhaps also in the normal situation, assumed to dictate the height velocity. These relations are shown in Fig. 3.

To explain a height velocity above the statistical limits of normality for age as observed in catch-up growth, a situation as shown in Fig. 4 is supposed to occur. At the onset of therapy after a period of growth restriction, the mismatch between actual size and target size (M2) is greater than the expected mismatch (M1). More receptors of the time tally are unsatisfied, and consequently the growth rate increases, thus leading to catch-up growth. As the original curve is reapproached, the degree of mismatch diminishes, the amount of unsatisfied receptors decreases, and catch-up growth slows down. Tanner argued that incomplete catch-up growth might occur if growth had been slowed too long, and that this might be due to a resetting of the time tally to a lower level.

The actual adjustment of growth rate, Tanner proposed, would be realized by a systemic factor, circulating within the blood to all parts of the body. The argument for this factor to be a systemic one was that during a typical catch-up the whole organism grows rapidly in approximately a propor-

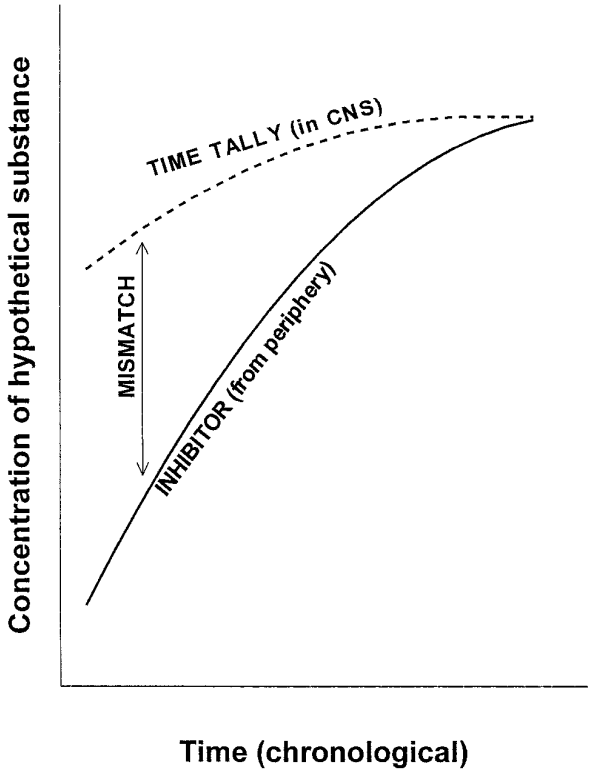

FIG. 3. Hypothetical relations underlying the mechanism of growth-control. [Adapted from J. M. Tanner: *Nature* 199:845–850, 1963 (122) © Macmillan Magazines Limited.]

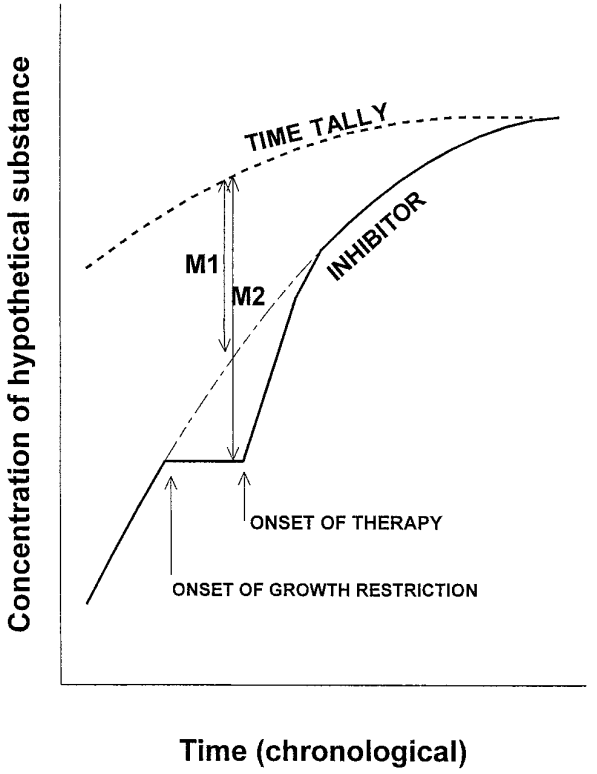

FIG. 4. Explanation of increased height velocity in catch-up growth. [Adapted from J. M. Tanner: *Nature* 199:845–850, 1963 (122). © Macmillan Magazines Limited.]

tionate manner. The precise identity of the systemic growth-stimulating factor was unknown but thought to be a balance of several hormones, released or coordinated by the pituitary.

As Tanner frankly admitted, this whole neuroendocrine model was speculative, but he presented it for testing, since one of the reasons for relative neglect of experimental work on growth, in his opinion, seemed to be the lack of appropriate models.

1. Target size. In the years after the initial postulation of this neuroendocrine hypothesis, the next results of rat experiments have been regarded as support for the existence of a centrally located representation of the target size, or "age-appropriate set-point for body size," as Mosier preferred to call it:

(a) After an electrolytic lesion of the dorsomedial hypothalamic nuclei, rats showed a proportional reduction of body size, while the pulsatile pattern and peaks of GH secretion as well as insulin concentrations were not reduced (123). Rats that had been severely food-restricted and then received such dorsomedial hypothalamic nuclei lesions, were still able to perform a normal catch-up spurt but only to the reduced size of nonfasted rats with the same hypothalamic lesions (124).

(b) After bilateral neonatal head irradiation, rats showed a diminished growth rate, irrespective of whether the entire head or only a narrow midline band had been irradiated (125–127), while pituitary concentrations of bioassayable GH, gonadotropin, and TSH were not significantly diminished (128). After an additional period of fasting these head-irradiated rats showed catch-up growth, but only to the smaller size of nonfasted irradiated rats (129).

(c) After high-dose cortisone treatment, rats showed a permanent stunting of body size (32), while GH secretion was elevated during the recovery period (130). After an additional period of fasting the cortisone-treated rats were still able to exert some catch-up growth, but only to the smaller size of nonfasted cortisone-treated controls (102).

In Mosier's view, these findings are all in line with Tanner's model and suggest that the rat possesses an age-dependent set-point mechanism for body size, probably located within a narrow midline band in the central nervous system, which is reset to a lower level by neonatal head irradiation and glucocorticoid treatment (131).

However, in our view, an alternative interpretation of the results of the experiments mentioned in paragraphs (a), (b) and (c) is possible: instead of illustrating an alteration of the set-point for body size, these experiments might merely be examples of incomplete catch-up growth due to a failure to fully restore normal conditions and remove all linear growth-inhibiting factors. Evidence for this alternative explanation is derived 1) from the observation that the rats described in paragraph (a) with lesions of the dorsomedial hypothalamic nuclei show permanent hypophagia and hypodipsia (123); 2) from the knowledge that cranial irradiation is accompanied by a high incidence of hypopituitarism and GH deficiency (132, 133) and the finding of Mosier himself who recognized that rats, who had received head irradiation in the neonatal

period as described in paragraph (b), showed a reduced integrated GH secretion afterward (134); and finally 3) from the knowledge that failure of catch-up after cortisone treatment has frequently been considered to be a consequence of a failure of response of target tissues to growth factors, possibly due to permanent changes in the morphology of the growth plate cartilage (32, 96).

Even if we assume that our alternative interpretation of their results is false, and consider the experimental data of studies of Mosier and Bernardis as solid evidence in favor of a central set-point mechanism for body size, it must be questioned whether this set point includes both weight and height or only weight. This question has become increasingly important since the recent identification of the *ob* gene and its adipocyte-specific protein leptin has provided the first physiological link to the existence of a regulatory system controlling body weight (135–138). Although the weight-regulatory system has not yet been completely elucidated, it seems to show much resemblance to the neuroendocrine model for the regulation of catch-up growth in height as proposed by Tanner. The weight-regulatory system is assumed to comprise 1) a central structure (the satiety centers in the hypothalamus) corresponding to Tanner's receptors of the "time tally," 2) a feedback signal (the adipocyte-specific protein leptin) comparable to Tanner's circulating inhibitor factor, and 3) an efferent signal (appetite and energy expenditure).

2. Actual size. The concept of inhibitor substances whose concentration would reflect the actual body size of an organism, as proposed by Tanner, was derived from a fundamental, theoretical paper providing a mathematical description of growth control. In this paper Weiss and Kavanau (139) suggested that each growing tissue produces specific chemical inhibitors that diffuse out into the blood and inhibit growth of the same tissue elsewhere in the body by acting at a peripheral level. Each tissue would thus have a feedback mechanism regulating its own size. Tanner used a slightly modified version of this view by assuming that the inhibitors do not act in the periphery, but instead provide a feedback signal to a central level, probably somewhere in the brain.

Although the concept of inhibitors appears theoretically sound, these substances were purely hypothetical, as neither origin nor site of action was known. In fact, although sporadic data suggesting their presence have been published (140), direct evidence supporting the existence of growth-inhibiting factors is not available. Moreover, some of the substances that have been previously regarded as growth-inhibiting fractions of human serum might have been IGF binding proteins (141). These IGF binding proteins can inhibit growth by suppression of the cellular effects of IGF. However, it seems highly questionable whether or not these proteins act in a way similar to the inhibitors in the neuroendocrine model. Altogether, the concept of inhibitors as proposed by Tanner still seems merely hypothetical.

3. Adjustment of growth rate. In the neuroendocrine model, the adjustment of height velocity is supposed to be brought about by systemic stimulation, probably via pituitary hormones. GH would be one of the most likely hormonal candidates to establish this stimulation. However, although not all elements of the somatotrophic axis have yet been fully explored during catch-up growth, it will be shown in *Section V* (see page 655) that there is, in fact, no solid evidence for an obvious increase of GH secretion, or enhanced action of any of the other factors of the somatotrophic axis, during catch-up growth. Moreover, it appears highly unlikely that the increase of height velocity in catch-up growth can be explained by an isolated increase of the basal serum levels of thyroid hormone, gonadal steroids, or insulin, because one would expect clinical symptoms of hormonal excess if one of these hormones is produced in amounts that double the normal height velocity. Therefore, the question as to how the systemic stimulation of catch-up growth would have to take place remains unanswered.

In summary, we can state that, although the neuroendocrine hypothesis appears to be an attractive model for the regulation of catch-up growth in height and has been republished several times (142, 143), the experimental evidence for the true existence of any of the components of this model, today more than 30 yr after its postulation, is still weak. This contrasts with the accumulating evidence favoring the existence of an analogous system regulating body weight. Therefore, it is not surprising that a new concept for the regulation of catch-up growth in height has recently been proposed.

B. The growth plate hypothesis

In 1994, Baron *et al.* (144) put forward the idea that the mechanism governing catch-up growth resides not in the central nervous system but rather in the growth plate. This hypothesis, which we will describe as the "growth plate hypothesis," is based on their observation that *in vivo* suppression of growth within a single growth plate of a rabbit by local administration of glucocorticoids was followed by local catch-up growth. As the catch-up was unilateral and restricted to the affected growth plate, it could not be explained by the neuroendocrine hypothesis. A neuroendocrine mechanism, or any systemic mechanism that involved circulating factors, would have affected all growth plates. Although Baron *et al.* did not exclude the possibility that both local and systemic mechanisms may contribute to catch-up growth in other circumstances, they have suggested that the mechanism for catch-up growth is intrinsic to the growth plate and proposed the following mechanism (144):

The chondrocyte at the epiphyseal end of the proliferative column in the growth plate serves as a stem cell. During normal growth plate senescence, the proliferative rate of the growth plate chondrocytes diminishes with each successive stem cell cycle. Hence, as the cumulative number of stem cell divisions increases, the proliferative rate, and thus the rate of longitudinal bone growth, declines.

Glucocorticoids suppress the proliferation of growth plate chondrocytes, probably of both stem and nonstem daughter cells. After cessation of local glucocorticoid administration, the cumulative number of stem cell divisions in the affected growth plate is therefore lower than that of non-glucocorticoid-exposed stem cells in the contralateral growth plate. Therefore the cells in the affected growth plate begin to proliferate faster than the nonexposed cells, thus leading to

local catch-up growth. Catch-up growth thus arises from a delay in normal growth plate senescence.

Incomplete catch-up growth is explained by an irreversible loss of linear growth arising from a decreased clone size per stem cell. By suppressing the proliferation of nonstem daughter cells, glucocorticoids may decrease the number of hypertrophic chondrocytes originating from each stem cell division.

In this theory, the only role for systemic factors would thus be permissive in the sense that they have to provide adequate environmental conditions allowing optimal growth.

Baron's theory is consistent with an old concept proposed in 1914 by Osborne and Mendel (145). They showed that prolonged food restriction in the rat was followed by growth at an age clearly beyond the normal growth period. Based on this observation, they suggested that the capacity to grow is only lost by the exercise of this fundamental property. In their opinion, growth thus only ceases when the growing tissues have grown as much or as long as their intrinsic capacity has allowed them to grow.

In fact, the growth plate hypothesis shows much resemblance to the ideas put forward by Williams and associates (5, 6, 31, 146), who carried out a series of experiments to analyze parts of Tanner's hypothesis. Williams showed that, while catch-up growth appears to be a whole body response, the various parts of the body seem to respond in an individual manner within the same animal, suggesting that there is no single mechanism regulating catch-up growth. Based on his findings, Williams, although being one of Professor Tanner's co-workers, worded a general theory for catch-up growth that differs from the neuroendocrine hypothesis. According to Williams, growth is a cellular phenomenon in which the cell has a program and a mechanism to recognize where it is in that program; if it is diverted from the program, then a stabilizing mechanism will tend to return it to the right course. The cells of a given tissue type have the same program and are coordinated by tissue-specific diffusable agents. The tissues and organs are coordinated at the program level and by permissive hormones such as GH (6).

V. Determinants of Normal Growth and Their Changes During Catch-up Growth

A. Introduction

Although genetic, ethnic, psychological, and nutritional factors also affect statural growth, it seems likely that hormonal factors, especially the somatotrophic axis (see Fig. 5) and the epiphyseal growth plate, are of greater importance in catch-up growth. Therefore, we will focus on these parameters in the following paragraphs. In advance, we must emphasize that the analysis of the role of the somatotrophic axis in catch-up growth is hindered, mainly for two reasons. First, a search of the literature has revealed no systematic

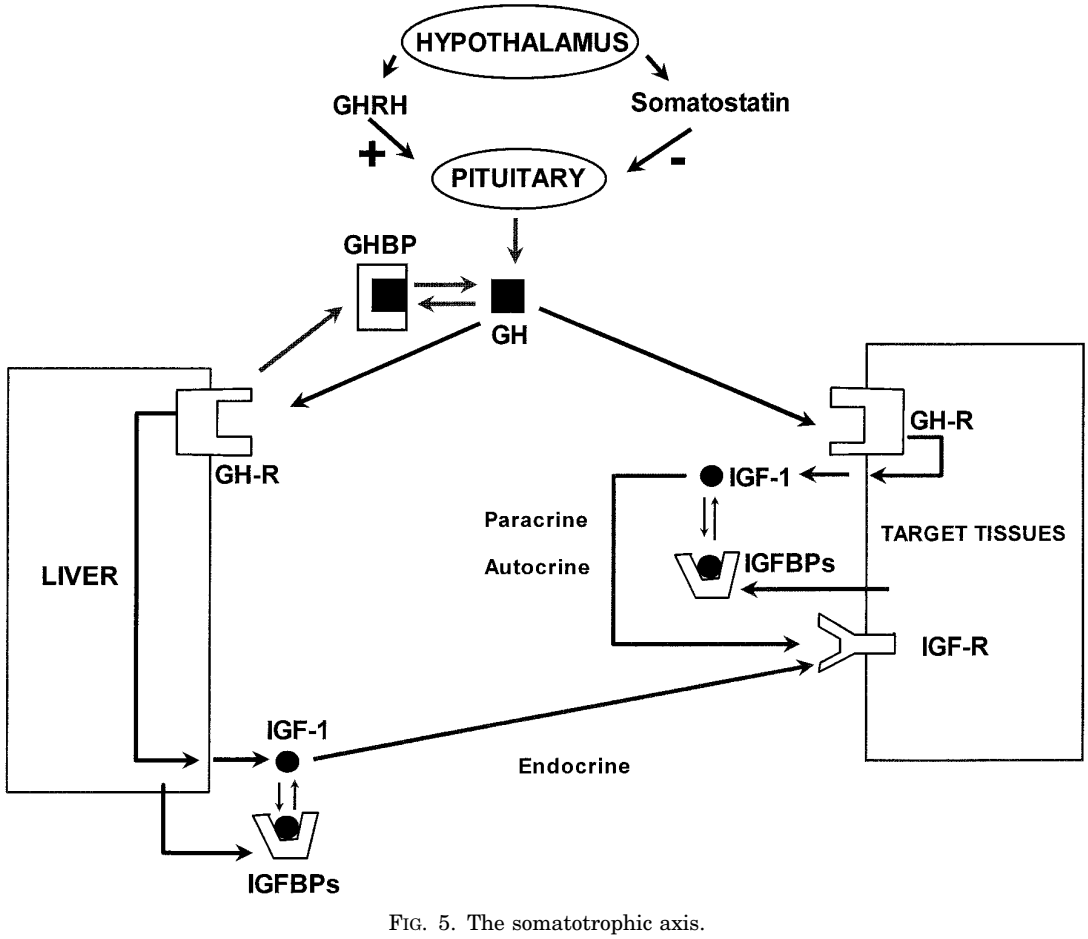

FIG. 5. The somatotrophic axis.

human study investigating the possible link between the somatotrophic axis and catch-up growth, and, second, the results from animal experiments cannot be extrapolated directly to the human situation.

B. The somatotrophic axis

1. GH-releasing hormone and somatostatin. Data on the levels of those two parameters during catch-up growth are scarce. In one of the few studies, rats food-deprived for 72 h showed a significant weight loss and a 80% reduction in prepro-GH-releasing hormone mRNA levels. Upon refeeding, body weight was restored and prepro-GH-releasing hormone mRNA levels became normal again (147).

2. GH. Data on GH secretion in man during catch-up growth are limited. In a patient who showed impressive catch-up growth after successful treatment of constrictive pericarditis, the maximum GH level in an arginine tolerance test was lowered before treatment and increased to a normal level during catch-up growth (148). In a considerable proportion of children with psychosocial short stature, an insufficiency of GH secretion has been demonstrated (59). On removal from the stressful environment, GH secretion reverts to normal (54, 60) and catch-up growth follows (57, 58). In children with marasmus, kwashiorkor, or marasmic-kwashiorkor, basal GH levels were elevated (149, 150), while GH responses to arginine tolerance tests were depressed (149) on admission to the hospital. During recovery, GH levels returned to normal (149, 150). In children with severe hypothyroidism, a reduced GH secretion has been found, which returns to normal after onset of replacement therapy (82, 83).

In older animal experiments, high serum levels of GH during catch-up growth were reported. During refeeding, after a period of undernourishment in the suckling period, an increase of pituitary size and GH content, as well as elevated levels of serum GH, was found in rats (151). Also during recovery from transitory growth arrest in the post-weaning period, increased GH levels have been demonstrated (90, 152, 153). The most distinct GH increase was seen after fasting and after cortisone injections (152, 153), but also after propylthiouracil-induced hypothyroidism a rise of GH levels was found (90). In hamsters, serum GH concentrations were also increased during accelerated growth after chronic food restriction (154). However, the value of these results is controversial because the GH measurements were mainly performed in trunk blood after death, whereas 24-h profiles would have given a more realistic reflection of GH secretion.

In later animal experiments, frequent sampling via a chronically implanted catheter was performed, allowing analysis of the pulsatile pattern of GH secretion (103, 130, 155). In rats, elevated peak GH values were found within the normal periodic pattern of GH secretion, during catch-up growth after fasting (155), and after cortisone injections (130). However, in rats that were first permanently stunted by x-irradiation of the head in the neonatal period, and subsequently subjected to an additional period of food deprivation, a catch-up growth acceleration to the stunted size of irradiated, nonfasted controls was found, without an accompanying increase of GH secretion (125, 126, 129, 156–158). In primates, an increase in stimulated mean GH peak levels during catch-up growth after corticosteroid-induced growth arrest was found (103). However, mean GH peak levels and GH area under the curve after insulin stimulation, as well as mean spontaneous GH secretion, did not increase during the catch-up period.

In summary, convincing evidence for an overt increase of GH secretion to a supranormal level during catch-up growth has never been given, either in man or in animals.

3. GH-binding proteins (GHBPs) and GH receptor. Although the insights into the physiology of the rather recently discovered GHBPs have been enlarged by studies in various clinical conditions (159–162), the exact function of GHBPs in normal growth and their possible role in catch-up growth has remained still far from fully understood. Unfortunately, the same also applies for the GH receptor. Since concrete evidence for an increased GH secretion is lacking, one could assume that catch-up growth might be caused by an increase of GH sensitivity, due to an increased number of GH receptors. However, this assumption is purely hypothetical, and even the correlation between tissue GH sensitivity and GH receptor levels is not as tight as one might expect. The latter is illustrated by a recent study in which glucocorticoids were administered to rabbits (163). As glucocorticoids are thought to inhibit linear growth at least partially by rendering target tissues insensitive to GH, one might expect to find a decreased number of GH receptors. However, to the surprise of the investigators, GH receptor mRNA levels in liver and growth plate actually increased.

4. IGFs. IGF concentrations are reduced in malnutrition, probably by virtue of a resistance to GH action (164), both in man (149, 150, 160, 165) and in rats (166, 167). In both species, a rapid normalization of IGFs is observed during nutritional rehabilitation (90, 149, 166–170). Sometimes, even a brief, transient overshoot to supranormal IGF levels is found (168, 171), possibly indicating that refeeding improves the capacity to synthesize IGFs more rapidly than tissue responsiveness to IGFs.

Several other factors are also known to influence IGF levels. Hypothyroidism causes a reduction of serum IGF-I levels and low IGF bioactivity in man (83, 172) and in rats (84, 90). After T_4 replacement therapy, a rapid normalization of IGF levels is seen, without overshoot (83, 84, 90). Cortisone treatment induces a significant reduction in serum somatomedin activity in rats, which returns to the control level by 21 days of recovery (152).

While showing that IGF may normalize during recovery, the above described observations suggest that a sustained, supranormal elevation of IGF levels during catch-up growth is unlikely. A finding indicating that the link between catch-up growth and circulating IGF levels is indeed not very tight, is provided by a case report of a child with a combination of Laron-type dwarfism and chronic malnutrition (173). During a period of hyperalimentation, this child showed clear catch-up growth, while IGF levels remained very low (173). Moreover, the absence of sustained, elevated IGF levels also seem to support the view that it is unlikely for the "upstream" components of the somatotrophic axis, such

as GnRH, somatostatin, GH, GHBPs, and GH receptor, to play an important role in the stimulation of catch-up growth.

5. IGF binding proteins and IGF receptors. The IGFs are present in the circulation and throughout the extracellular space almost entirely bound to the members of a family of high-affinity IGF binding proteins, of which six different subtypes have so far been identified (174). The IGF-binding proteins have a variety of functions, including prolongation of the serum half-life of the IGFs, transportation of the IGFs to target cells, and modulation of the interaction of the IGFs with their surface membrane receptors (175). Although there are two known receptors that specifically recognize the IGFs, the majority of the physiological actions of the IGFs are believed to occur by activation of the IGF-I receptor. The *in vivo* status of the IGF-I receptor is extremely dependent on the local and circulating levels of IGF-I. Generally, increasing IGF-I concentrations cause a decrease in receptor number (176). At this time, no specific studies have been performed on IGF-binding proteins or IGF receptors in catch-up growth.

C. The epiphyseal growth plate

The epiphyseal growth plate is the ultimate target organ of the above described growth-regulating mechanisms. The epiphyseal growth plates are located in the proximal and distal parts of the long bones and have a strict cellular organization according to stage of maturation, with germinative, proliferative, hypertrophic, and degenerative cell layers (see Fig. 6).

The germinative cell layer consists of stem cells or progenitor cells, which rarely divide. During the process of longitudinal bone growth, stem cells enter the proliferative cell layer and begin to divide frequently, forming continuous cell columns parallel to the longitudinal axis of the bone. Subsequently, these cells stop dividing, mature, and become part of the hypertrophic cell layer (177). Finally, in the zone of calcification, cartilaginous matrix is transformed into bone matrix. It is not yet clear whether terminally differentiated chondrocytes survive this transformation and subsist as osteoblasts or undergo apoptosis. Longitudinal bone growth is thus the result of recruitment of new progenitor cells from the stem cell layer and the number of cell divisions in the proliferative layer together with the increasing size of cells in the hypertrophic layer. As new stem cells continuously start their program of differentiation, the growth plate could be considered as a constantly renewing tissue, pushing the bony epiphysis further and further away from the center of the long bone.

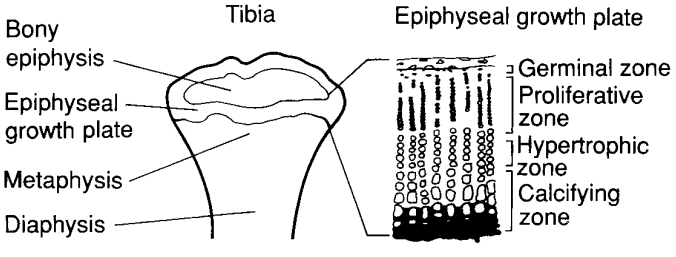

FIG. 6. Schematic representation of the proximal epiphyseal growth plate and its cellular organization in the rat. [Reproduced with permission from C. Ohlsson *et al.*: *Acta Paediatr [Suppl]* 391:33–40, 1993 (177).]

In rats, 4 days of fasting resulted in a decrease of the width of the epiphyseal cartilage plate and a reduction of the number of cartilage cell rows as well as the cells per column. Upon refeeding, the width of the epiphyseal cartilage plate started to increase rapidly and became normal after 8 days (178).

Lewinson *et al.* evaluated the morphological changes in tibial growth plate cartilage (179) and in the mandibular condyle (180) in female rats, rendered hypothyroid by methimazole, as well as the respective effects of T_4 and GH administration *in vivo*. Hypothyroidism of 7 weeks duration brought about a decrease of 27% of the width of the epiphyseal growth plate cartilage and caused significant changes in the histology of the condylar cartilage. Administration of GH alone failed to reverse the defects caused by hypothyroidism, whereas treatment with T_4 resulted in full recovery of cartilage cellularity and morphology of both growth centers.

These findings suggest that short-term malnutrition and hypothyroidism induce no permanent damage to the growth plate cartilage. Probably because there is no technique available of direct *in vivo* observation of the growth plate, there is a lack of data on changes occurring in the human growth plate during catch-up growth.

VI. Concluding Remarks

Catch-up growth is a fascinating, long known but still poorly understood, biological phenomenon that clearly illustrates the strong intrinsic power of a child to maintain its predetermined track of growth.

The variability of catch-up growth, not only among diseases but also among individuals with the same disorder, suggests that influences on catch-up growth are multifactorial. Nature, intensity, and duration of the preceding growth disorder as well as efficacy of therapy and age at onset of therapy constitute major influencing factors.

Although height velocity may reach a level several times above the normal limits for age or maturity during catch-up growth, definite proof of an increase of autocrine, paracrine, or endocrine determinants of normal growth to supranormal levels is not available.

The evidence in favor of the neuroendocrine hypothesis appears to be weakening, and the growth plate hypothesis seems a more promising model for the mechanism of catch-up growth, although further experimental evidence is required.

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