Endocrine Control of Growth

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It is generally accepted that adequate nutrition is a prerequisite for normal postnatal growth. Hormones such as growth hormone (GH), insulin, thyroxine, and sex steroids play a pivotal role in controlling musculoskeletal growth, as proven in a number of well-described clinical conditions (Fig. 1). However, it has been observed that the \textit{in vitro} stimulatory effect of hormones on cell metabolism or cell multiplication is often less impressive than their \textit{in vivo} effect, suggesting that their action at the cellular level could involve other factors. This led to the discovery of many cell growth factors. The most extensive studies concerned the somatomedins (Sm) or insulin-like growth factors (IGF) isolated from human plasma and believed to mediate the growth-promoting action of GH. The measurement of their concentration in tissue, biological fluid, and principally in blood provided numerous data concerning growth and nutrition in various clinical conditions.

In a developmental perspective, growth regulation, particularly the regulation of skeletal growth, presents considerable differences according to age from the perinatal period to adolescence. Hormonal changes play an important role in the adaptation to nutritional alterations by limiting the growth rate. Their role in catch-up growth is still under investigation.

GROWTH HORMONE AND SOMATOMEDINS

A major difference between pre- and postnatal life is the switch, at the time of or just before birth, to the GH dependence of statural growth. At the same time it can be hypothesized that there is a shift from an autocrine or paracrine to a more endocrine type of control of growth. In fact, after birth the events that control skeletal growth and more specifically cartilage activity are largely dependent on GH, although there is presently some debate on the significance of experiments that showed a direct effect of GH on this tissue.

Control of Growth Hormone Secretion

Growth hormone secretion is regulated by both stimulatory and inhibitory factors of hypothalamic origin. Growth hormone-releasing factor (GRF) is well iden-
FIG. 1. Schematic representation of growth rate and levels of the main circulating hormones from birth until adolescence. dheas, dehydroepiandrosterone sulfate.

tified among the first group, and somatostatin (SRIF) belongs to the latter. The availability of human GRF for clinical studies and eventually for therapeutic use has stimulated much interest in this area. Presently much has been done to evaluate the somatotrophic cell responsiveness to GRF. The relationship that exists between hypothalamic regulation of GH secretion and changes in growth rate in relation to age and sex has also attracted much attention.

Much of our knowledge of the physiological roles of endogenous somatostatin and GRF in the control of GH secretion has been provided by experimental studies on the rat (1,2). The elegant studies of Tannenbaum and Ling in freely moving rats demonstrated that the episodic pulses of GH secretion in male rats were partly dependent on episodic release of GRF and, more importantly, related to the intermittent withdrawal of a tonic inhibition of GH secretion by hypothalamic somatostatin (3). Similar findings in humans are consistent with this hypothesis, as intermittent pulsatile GH secretion was observed during human GRF (hGRF) infusion (4). Further evidence that endogenous somatostatin in the rat plays a role in controlling GH secretion is provided by the administration of somatostatin antiserum, which reverses the inhibition of GH secretion induced by starvation and streptozotocin diabetes (5,6). In fact, tonic somatostatin inhibition has been postulated in man during starvation. This could in part explain the elevated concentrations of circulating GH that are frequently found in malnutrition. The concentration of cir-
culating IGF I could also be involved in this feedback. This peptide stimulates somatostatin release from rat hypothalami in vitro (7) and exerts a potent direct inhibitory effect on GRF-stimulated GH release in cultured pituitary cells (8). Low circulating values of IGF_I are observed in contrast to the high concentrations of GH in Laron-type dwarfism as well as in children with kwashiorkor (9). There is also strong evidence that GH itself is capable of regulating its own secretion through a short-loop feedback mechanism (10,11).

Furthermore, it has been shown, at least in rats, that the normal GH response to GRF is not a simple phenomenon (12): glucocorticoids enhance the GH response to GRF, probably by modulating the pituitary sensitivity; similarly, testosterone increases the GH response, but estrogens do not; and chronic hypothyroidism inhibits the GH response to GRF in vivo. Therefore, the whole endocrine status of the animal must be considered when evaluating the GH response to GRF. To what extent this can be applied to the child remains to be seen.

**Growth Hormone Secretion in Relation to Age and Puberty**

Plasma GH levels are higher in fetuses and newborns than in later life. Growth hormone does not play a central role in the control of growth in the fetus. In only a few isolated cases of complete genetic deficiency of GH and/or IGF I may a moderate growth retardation occur in utero. Fetal GH deficiency can therefore be largely compensated by other growth-stimulating mechanisms. However, in cases with complete GH deficiency, cessation of growth is observed during the early weeks following birth (Fig. 2). This indicates that GH takes over the control of

![FIG. 2. Early growth retardation in two children with the clinical features of complete GH deficiency caused either by GH gene deletion or by absence of somatomedin generation (Laron-type dwarfism).](image-url)
growth in extrauterine life. The so-called "basal GH values," more precisely the episodic pattern of plasma GH concentrations, is changing at the time of puberty under the influence of gonadal steroids. Recently it was shown that puberty, at least in boys, is accompanied by an increase in GH pulse height and frequency, although considerable individual variations were observed (13). The stimulatory effect of estrogens, although less convincing in physiological conditions, is also likely to occur, as mean plasma GH levels are higher in women than in adult men (14). It can therefore be firmly concluded that GH secretion is stimulated by sex steroids and plays a major role in the pubertal growth spurt.

During the first semester of life, infants present with a pubertal-like spurt of testosterone secretion and, although to a lesser extent, of estradiol. These steroids might play a role in the maintenance of higher GH levels in neonates. The effect of these on skeletal growth, if it occurs in infants, is probably blunted in the presence of an already maximal, although decelerating, growth rate. Precise longitudinal studies have shown that boys grow faster than girls during the first part of the first year, coincidentally with elevated plasma testosterone levels. However, acceleration of bone age does not occur at that time (14).

Clinical Assessment of Growth Hormone Secretion: Difficulties and Limits

Because of large age-dependent inter- and intraindividual variations in the 24-hr profile of plasma GH concentrations, there is no simple way to assess GH secretion routinely in physiological conditions. There are strict methodological and practical requirements for this evaluation during physical exercise or during sleep. Preliminary data have shown a positive relationship between height and the integrated 24-hr GH concentration in healthy children (15). For practical reasons, GH secretion is commonly estimated by the response to pharmacological stimulation including the injection of synthetic human GRF.

In children with retarded growth, when pituitary dwarfism has been ruled out, there remains, according to the degree of GH response to stimulation, a spectrum of clinical conditions ranging from normal pituitary function to overt hypopituitarism. To what extent the degree of responsiveness can be correlated with the individual growth rate remains unclear. Furthermore, the usefulness of this evaluation in deciding to use human growth hormone (hGH) or GRF therapy in nonhypopituitary children is questionable, as it does not make it possible to predict the growth response. Other factors such as the nutritional status and the age of the child might influence the response to hGH, as observed in hypopituitary children.

In the normal child with short stature, there is some evidence that a prepubertal transient decrease of GH secretion may contribute to growth retardation and cause pubertal delay (16). Whether such children would benefit from hGH administration remains to be demonstrated by long-term studies.

Growth Hormone Deficiency

The availability of hGRF to test the pituitary response was expected to facilitate greatly the differential diagnosis between GH deficiency of pituitary and hypo-
lamic origin. This has turned out to be an oversimplification. A tentative classification, maintaining that approach, of conditions with GH deficiency has been proposed. It takes into account other aspects of GH/somatomedin regulation:

1. Neuroendocrine control: the hypothalamic and pituitary regulation of GH secretion.
2. Cellular response to GH: the effect of GH on somatomedin-producing tissues, principally the liver. This effect depends on the binding of GH to its receptors, postreceptor events, and IGF production. It is largely influenced by nutrition.
3. The equilibrium between the circulating somatomedins and peptides acting as inhibitors of the somatomedin activity. This equilibrium is closely related to the nutritional status.
4. The cellular response to somatomedins and hormones in skeletal tissues such as cartilage and bone.

It is beyond the scope of this chapter to comment on the efficacy of hGH therapy in hypopituitary children (17). However, from the many studies evaluating the effects of hGH, it is remarkable that complete catch-up growth is seldom achieved, as would be expected from a fully substitutive therapy (as, for example, in hypothyroidism). Several factors could explain this situation: (a) our inability to mimic fully the true episodic GH secretion, which, at least in the animal, has been shown to be necessary for normal growth; (b) the occurrence of permanent cartilage lesions caused by GH deficiency; however, this has not been demonstrated in animals; (c) one could also speculate on the metabolic and nutritional condition of the children—it is known that hGH administration cannot accelerate the growth rate in extreme cases when calorie intake is insufficient; (d) growth response to hGH could be age related, as it decreases in older children when epiphyseal cartilage is close to fusion. However, quite unexpectedly, we did not observe a better catch-up growth in treated children with a bone age below 3 years than above (18). This inability to recover fully from severe growth retardation (greater than 2 SD) could simply reflect inadequate hGH therapy. Again, these poor results contrast with the full catch-up growth obtained in growth-retarded children with celiac disease when put on a gluten-free diet. They probably recover within a few weeks and have a normal cartilage responsiveness to the circulating somatomedin activity (Fig. 3).

![Diagram](image_url)

**FIG. 3.** Changes in GH secretion assessed by the response to the arginine-insulin tolerance test (AITT) and plasma somatomedin bioactivity in children with celiac disease before and after 3 months of gluten-free diet. The most consistent finding is the normal value of somatomedin activity in treated children.
Somatomedins and Growth

The somatomedins, also called insulin-like growth factors (IGF), are polypeptide growth factors named for their functional and structural similarity to insulin. They mediate the growth-promoting action of GH; they have an insulin-independent insulinomimetic effect on adipocytes and stimulate chondrocyte sulfation and cell multiplication in a variety of other cultured cell types. One of these, IGF I or SmC, stimulates skeletal growth when administered to hypopituitary rats (19). It is produced by the liver but has also been isolated from other tissues (20). Circulating levels and tissue content of this peptide in hypophysectomized rats definitely depend on GH (20). This again brings up the concept of paracrine and autocrine control of somatomedins reaching target cells to regulate growth and puts theoretical limits on the clinical significance of circulating SmC levels.

Measurements of IGF I by radioimmunoassay enable easy discrimination between acromegaly and hypopituitarism in adults (21). In children it is necessary to take into account factors such as age and puberty to define normal values. The IGF I concentrations are low at birth and correlate positively with birth weights. They remain in the low range during the first 2 years of life. This is surprising in view of the very high growth rates observed during this period. An increased target tissue "sensitivity" has therefore been suggested from studies on cartilage responsiveness in animals and on SmC receptors on circulating monocytes in newborns. It is also possible that during the early postnatal period the fetal paracrine control still has preeminence over endocrine control mechanisms. Plasma IGF I values increase progressively to adult values with a sharp but transient peak at the time of puberty in both sexes (22). As already mentioned for the pattern of pulsatile secretion of GH, there is also a significant correlation between IGF I levels and the stature of the child. This could partly account for the large cross-sectional age-related variations observed in normal children.

The clinical usefulness of IGF I measurements is quite limited. In children between 5 or 6 years of age, they do not give any information on the level of GH secretion. Only normal values are of diagnostic significance in older children, as plasma IGF I can be low in many pathological situations, particularly in undernutrition. In fact, IGF I evaluation has not become a routine technique. However, circulating IGF I values bear some significance by comparison with the level of GH secretion as usually assessed. High GH values contrasting with low IGF I levels are definitely suggestive of nutritional problems such as protein-calorie deficiency. Furthermore, it is not clear whether the IGF I levels should be interpreted with respect to chronological age or to developmental age expressed by bone age or stage of puberty. It may be preferable to use developmental age. Longitudinal studies need to be conducted to analyze the relationship between statural growth and circulating IGF I/SmC levels.

Finally, it is also worth mentioning that some hypopituitary children present with normal growth in the absence of GH secretion but with normal IGF I levels. Growth in these children may have been caused by obesity with hyperinsulinism.
and/or hyperprolactinemia (24). Other examples of discordance between growth rates and GH/SmC concentrations have been reported (25).

OTHER HORMONES INTERVENING IN SKELETAL GROWTH

The other hormones definitely differ, from a clinical point of view, in their effects on linear growth and bone maturation. Insulin seems to play a role closely similar to other cellular growth factors. Thyroxine is necessary for growth at all ages and has a major effect on bone maturation. The role of hydrocortisone at physiological levels is unclear. Sex steroids dramatically change the course of growth during puberty and accelerate the epiphyseal maturation.

Thyroxine

Thyroid hormones do not play a significant role in the linear skeletal growth of the fetus. As a matter of fact, newborns with thyroid aplasia are of normal size at birth. However, congenital hypothyroidism after birth results immediately in retarded growth (26). The major characteristic and consequence of fetal and postnatal hypothyroidism is the severe retardation of osseous development. Thyroxine (T4) and/or triiodothyronine (T3) have a permissive role on and influence the secretion of GH by the pituitary gland as well as the cellular response to somatomedin. Growth hormone does not stimulate growth in hypothyroid children in spite of an increase in SmC levels (27). The most important site of action of thyroid hormones therefore seems to be at the level of the cartilaginous growth plate (28).

Insulin

Insulin deficiency, as observed in inadequately treated diabetes mellitus and in malnutrition, is associated with growth failure (29). Increased insulin levels may contribute to accelerated growth in obese children. Most authors are of the opinion that the primary role of insulin is to regulate fuel homeostasis, enabling other factors to fully control linear growth.

Glucocorticoids

The role of hydrocortisone on growth in normal children is unknown. It has been shown, in pathological situations during treatment with glucocorticoids, that growth is impaired by a minimal excess of corticoid activity. This is largely because of a direct action of corticoids on the target tissue. Incomplete catch-up growth in some of these children is thus probably caused by permanent cartilage damage.
Sex Steroids

The stimulation of growth by gonadal sex steroids depends on the dosage and duration of administration. When given at pharmacological doses, they always cause a disproportionate stimulation of epiphyseal maturation. Their ultimate effect, before puberty, is loss of growth potential and diminished final height. Interestingly, when given at low doses, anabolic steroids, which are considered weak androgens, stimulate growth without modifying GH secretion or circulating SmC levels (30).

In the perinatal period boys grow faster than girls, but their skeletal maturation is slower (14). In view of the higher plasma levels of testosterone in boys, this could indicate that skeletal maturation in the perinatal period does not respond to testosterone (Table 1). This would fit the observation that newborns with congenital adrenal hyperplasia do not exhibit advanced bone age at birth.

Adrenal androgens, which are weak androgens, may be responsible for the mild growth spurt demonstrated at the age of 7 years, which is essentially an acceleration of the growth of the long bones (31).

Analysis of pubertal growth provides a model for the study of the interaction among GH, Sm, and gonadal steroids. Growth hormone plays an undoubtedly major role during puberty by causing the pubertal rise of IGF I. Androgens increase the amplitude of secretory pulses of GH (13). It is likely that estrogens similarly promote GH secretion in girls. There is also some evidence for a direct skeletal action of sex steroids: estrogens, given at very low doses, stimulate the growth of long bones in agonadal girls without modifying circulating IGF I levels (32); in Laron-type dwarfs, characterized by a genetic deficiency of IGF production, a pubertal growth spurt has been reported. More recently, in vitro studies in our laboratory have shown that estradiol and testosterone can stimulate chondrocyte

| TABLE 1. Sex differences in growth of infants: boys compared to girls * |
|---------------------------------|-----------------|-----------------|
|                                 | Length          | Weight          | Skinfolds |
| Distance                        |                 |                 | (subscap.)|
| Birth                           | ++              | +               | —         |
| 3 months                        | +++             | +++             | —         |
| 12 months                       | +++             | +++             | —         |
| Velocity                        |                 |                 |           |
| 0.5 month                       | —               | —               | —         |
| 2 month                         | ++              | +++             | +         |
| 7.5 month                       | 0               | +               | 0         |
| 10.5 month                      | 0               | 0               | 0         |

*Data adapted from the Zurich longitudinal growth study (14).
+ or — means significantly higher or lower values for boys than for girls.
0.001 <p <0.05.
metabolism in cultured cells taken from pubertal animals. Thus, the pubertal growth spurt might be caused by a complex sequence of events eventually modulated by the level of circulating steroids. In addition, a direct action of GH on epiphyseal cartilage has also been demonstrated in hypophysectomized rats (33). Growth hormone could play a role by stimulating local production of growth factors.

ENDOCRINE ADAPTATION TO NUTRITIONAL ALTERATION

Many studies and monographs have addressed this topic. Our comments are largely derived from the recent review article by Philipps and Unterman (34).

Growth Hormone and Somatomedin-C

Normal growth does not occur in malnutrition despite the presence of normal or increased circulating GH levels (Table 2). This apparent paradox is even more pronounced in protein deficiency. In addition, administration of GH does not benefit children with malnutrition. Acute starvation, chronic enteropathies such as celiac disease (Fig. 3), anorexia nervosa (Fig. 4), and of course protein deficiency and marasmus provide human models for the study of this situation. Anthropometric measurements such as skinfold thickness, arm circumference, body weight, and height changes as well as the measurement of plasma proteins, red blood cell counts, and bone mineralization have been used as indices of the nutritional deficiency. However, we still need a simple and reliable index that could be sensitive enough to detect minimal changes in the nutritional status. Plasma SmC/IGF I is a candidate for this role, especially in children with unexplained short stature whose nutritional status might be suboptimal. Severe malnutrition is associated with very low level of somatomedin by bioassay or SmC by radioimmunoassay and eventually with the presence of circulating sulfation inhibitory peptides. The changes in

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<th>TABLE 2. Clinical conditions characterized by low SmC/IGF I and normal or elevated GH secretion</th>
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<tr>
<td>Genetic absence of IGF/IGF₆ (Laron dwarfism)</td>
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<td>GH dependent dwarfism with normal immunoreactive GH</td>
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<td>Idiopathic short stature</td>
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<td>Starvation/suboptimal nutrition</td>
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<td>Acute starvation</td>
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<td>Low-calorie/low-protein diet</td>
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<td>Celiac disease</td>
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<td>Psychological dwarfism</td>
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<td>Anorexia nervosa</td>
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<td>Chronic nutritional deficiency</td>
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plasma SmC–IGF I levels during fasting correlate positively with changes in nitrogen balance (Fig. 5); they are unresponsive to hGH administration and increase dramatically during refeeding (35). It is likely that similar changes occur in chronic illnesses and kidney diseases, which are usually accompanied by comparable nutritional alterations. More remains to be done to evaluate the information provided by changes of SmC levels in different states of malnutrition of variable intensity (Fig. 6).

FIG. 4. Slowing down of growth in a girl with anorexia nervosa. Late weight gain was associated with pubertal onset and growth resumption. For several years, the patient exhibited low levels of somatomedin; furthermore, she did not respond to a hGH therapeutic trial (data not shown) performed at the age of 14 years. BA, bone age.

FIG. 5. Changes in plasma SmC/IGF₁ and cumulative nitrogen balance in response to nutritional therapy in six patients with Crohn's disease, relapsing pancreatitis, or postgastrectomy syndrome. (From Clemmons et al., ref. 35.)
Insulin

Hypoinsulinemia plays a role in the adjustment of the metabolic machinery to the growth failure induced by undernutrition. Insulin appears to be linked to the IGF system and to growth in many ways: it regulates cellular nutrition and may stimulate the release of growth factors by increasing the sensitivity to GH (36). Actually, changes in hepatic binding of the growth hormone under conditions of altered nutrition raise the possibility that this could be one of the mechanisms responsible for the changes in IGF I/SmC (37,38).

Cortisol

Catabolism may increase somewhat in marasmus because of the high cortisol levels observed in these patients. This might contribute to the increased loss of muscle protein in children given low-protein diets.

Thyroid

Reduced peripheral conversion of $T_4$ to $T_3$ is characteristic of starvation and chronic malnutrition. The organism, as it were, attempts to conserve energy by
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reducing metabolic expenditure. This is associated with an increased production of reverse T₃.

A paradoxical blunting of the release of thyroid-stimulating hormone in response to thyroid-releasing hormone is also observed. There is thus little evidence to support the diagnosis of hypothyroidism in malnutrition. However, the effects on growth of the low levels of T₃ have not been adequately documented yet. In view of the critical role of T₃ in the control of growth, these changes are probably important for survival.

CONCLUSION

The most important endocrinological findings in malnutrition relate to the GH—somatomedin system. Changes observed appear to be acute markers of change in nitrogen balance and energy intake. It appears likely that the binding capacity of GH binding sites, mainly in the liver, is one of the main regulating factors. This area of clinical investigation and experimental research shows promise as a means for evaluating the impact of nutrition on growth of children.

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**DISCUSSION**

**Dr. Martorell:** When you refer to undernutrition in developing countries, do you mean severe malnutrition? What evidence do we have that there are endocrine disturbances in milder forms of undernutrition and that these endocrine disturbances, if they exist, are involved in stunting?

**Dr. Rappaport:** Of course, many of the studies to which I referred are either acute studies on fasting or related to the problem of short stature, in which we still question whether nutritional factors play a role or not. How much are these models relevant to stunting in developing countries? It is difficult to answer that question, but I would imagine that stunting is associated with disturbances of the whole system that regulates skeletal growth, i.e., cartilage activity and bone formation. One of the long-lasting examples that we know of is anorexia nervosa. Anorexia nervosa sometimes occurs in young children, from 5 years onwards. We know that the hormones control growth from the very first weeks or months of life and that the same mechanisms (might) control growth before and after the age of 5. Thus, the same mechanisms could be responsible for growth retardation between the ages of 0 and 5 as well as after 5 years of age. Some children with anorexia nervosa present with total cessation of growth, sometimes as early as 8 years of age and eventually until the age of 19, and only at that time does growth resume if they gain weight and if puberty begins. I would thus assume that this model is appropriate.

**Dr. Golden:** We have recently been looking at somatomedin-C in Jamaican malnourished children. It follows closely the pattern you have described for patients with celiac disease: it is very low in malnourished children on admission, together with a very high growth hormone level, which comes down although the somatomedin doesn't start to rise for about 30 to 35 days in longitudinal measurements; then it goes up to really quite high levels. We couldn't demonstrate any difference between the somatomedin-C in edematous and non-edematous children. Dr. Smith recently brought specimens from Nigeria to Jamaica and analyzed them at the same time to try to get comparative data on somatomedin-C levels between the Nigerian marasmic kwashiorkor children and the Jamaican ones. She found exactly the same pattern in longitudinal samples taken from Nigeria and Jamaica.

**Dr. Milner:** It is nearly 20 years since we demonstrated, in the same unit, high GH and low plasma insulin levels and inappropriately low insulin responses to glucose and amino acid challenges (1,2). The loop of the circle has been closed as a result of recent work with rats (3). The maintenance of the GH receptor on the hepatocyte is insulin dependent, and this closes the conceptual circle, because if there is insulin deficiency and failure of maintenance of GH receptors on the hepatocyte, there is a block to GH making somatomedin.

**Dr. Rappaport:** Until recently all our interest lay in the changes in GH levels that we see in malnourished children: some have very low values, comparable to those found in
hypopituitarism, and some have very high values. Our interest has now shifted to the circulating growth factor, somatomedin (Sm-C/IGF-I), yet we don’t know exactly what its levels mean. We have to be very careful because we do not know exactly what the active and nonactive parts are in the circulating somatomedin that we measure. Somatomedin is bound to proteins, and we don’t know how much of it is really active; furthermore, at present we really don’t know exactly how the skeleton is able to pick up the somatomedin from the circulating blood in order to grow. There are data showing that local growth factors, including Sm-C, which are produced in many tissues and eventually in the cartilage, are of great importance in the regulation of its growth. So it might turn out that what we see in the blood does not have much relevance and that most of the events occur at a cellular level, in which case it is almost impossible to get an insight. Circulating cells and fibroblasts can be looked at, but we cannot perform biopsies of skeletal tissue in these patients. However, rat models do exist.

Dr. Gopalan: In a comparison of the pattern of adolescent growth in the malnourished and well-nourished, Tanner has made the point that menarche is delayed while the duration of the adolescent growth spurt is prolonged in the undernourished, with the result that they are allowed to grow, for example, until 19 years of age instead of 16 or 17 years, as in well-to-do populations. I would like to know the hormonal mechanism through which this is mediated.

Dr. Rappaport: I don’t know of a clear study on hormonal changes comparing these conditions. It has been shown that when the growth spurt occurs later in case of undernutrition or in case of spontaneous delay of puberty—again I don’t know to what extent these two conditions are similar—the growth spurt is somewhat less important, and the final height is the same as in normal adolescents. However, this is not relevant to all models. When pubertal growth is very much delayed, the total growth during puberty may not be as important as expected, and these patients might end up with a final height below normal. That is what we see in a small number of patients with anorexia nervosa: the total gain in height during the pubertal growth spurt is less when puberty occurs very late.

Dr. Nabarro: Several workers have noted that there are seasonal differences in the rates of weight gain and length increment in children. In our situation, weight gain appears to be greatest in the months around harvest, and length gain is greatest about 3 months later. We suspect that children with a small postharvest weight gain rate also have a low rate of length increment. Perhaps children are resistant to GH during the preharvest month and need to gain weight subsequently to overcome this resistance and develop adequate somatomedin levels for increased skeletal growth. This would explain the observed interval of about 2 to 3 months between the period of greatest weight gain and the period of greatest height increment.

Dr. Rappaport: I cannot go that far. Your example is unique because we don’t have many opportunities to relate these events, weight and height gain, over the years at a population level. One might hypothesize that in your model we could find the sequence of changes in GH and somatomedin that has been described in acute conditions. The point is whether studies of circulating somatomedin would provide more information. Some believe that it is a very sensitive index and that it could be used to monitor very precisely the adequacy of the nutritional supply. However, we are still at the very beginning of using this parameter, and I would not be overenthusiastic about it.

Dr. Martorell: In Bangladesh, it seems to me that what children did first when the food situation improved was to put on weight because they had a low weight for height, and after they had achieved that, then they grew in length. Is that the same as you found?
Dr. Nabarro: Identical. It is about 2 months earlier where we are working than in Bangladesh, but that is because the harvest takes places 2 months earlier.

Dr. Rappaport: May I make a comment on the question of low weight for height. I am still puzzled by the condition in which weight for height is normal and yet the children are undernourished. Here again I come back to the models that I know, although I am not sure that they are relevant in other situations—celiac disease for example. Celiac disease presents itself in two ways. Either it is an acute disease that is clinically diagnosed during the first months of life; these children have diarrhea and are underweight, in which case there is no problem. Or, quite a number of children present with just normal weight for height and look like hypopituitary children. Celiac disease in these children is diagnosed at 5, 6, or 7 years of age, and in fact they are investigated because they are very short. That is puzzling to me for two reasons. First, I don’t know how they achieve this equilibrium between weight and height, and sometimes they are even slightly fat; second, several studies have been done—a Belgian group (4) found consistently low values of GH secretion in these children, as in hypopituitarism. In our experience, 80% of the children we have been able to study had normal or high levels of GH (5). Thus, GH secretion is probably extremely variable according to age or to other factors that I don’t know about. We can only speculate that all these children have probably an impaired “production” of cellular growth factors. Malnourished children frequently present with normal weight for height. What does a normal weight for height mean, compared to low weight for height, in terms of risk or metabolic balance? It seems to me that hormonal changes are just superimposed, but I don’t think they explain what is happening.

Dr. Tomkins: You mentioned two studies on GH in celiac disease, yours and someone else’s, which showed different results. Could the difference not be attributed to differences in food intake in the week preceding the measurement? Quite a number of studies in celiac disease have shown a profound decrease in food intake (30%), certainly in teenagers and adults, comparable to the poor nutrient intake in chronic diarrhea, which is indeed associated with longitudinal growth faltering. What do you think is the effect of differences in food intake as opposed to nutritional status, weight for height, or height for age? Could these explain the differences?

Dr. Rappaport: That is a good point. I have absolutely no data on the food intake at the time of the study in either case. All I can say is that none of these children had any diarrhea at the time of the study. Thus, the mechanisms explaining the limitation of the nutrient supply, which I suppose exists in these children, is still unclear.

Dr. Hernandez: Do you have any data about the 24-hr secretion of GH in these celiac patients or about the response to the GRF stimulus?

Dr. Rappaport: I have no data on the 24-hr secretion of GH in these patients. Regarding your second question, a Chilean study showed that the response to GRF in undernourished children was normal, but I don’t know exactly the details of the population that was studied.

Dr. Waterlow: I found fascinating the attempt in the discussion to see how we could bring Professor Rappaport’s models, which are basically clinical, close to those of the Third World. This has given us a tremendous stimulus to look for an appropriate model in the light of the data Dr. Rappaport describes. What about the effect on growth of mild iodine deficiency, which is very common throughout large parts of Asia, Africa, and South America? Of course, severely iodine-deficient infants present with stunted growth. What, however, is the effect of mild iodine deficiency and reduced thyroid hormone production on the growth factors you have been discussing?
Dr. Rappaport: Extreme situations are much better documented than milder deficiencies. Extreme hypothyroidism induces GH deficiency and eventually also somatomedin deficiency, which is probably secondary to GH deficiency. When a hypothyroid child is treated with thyroid hormone, he thereafter has a normal GH secretion. However, it is not clear whether catch-up growth, which is very rapid in the treated hypothyroid child, occurs prior to normalization of GH secretion and somatomedin levels. There are very few data, especially longitudinal data, on this aspect.

Dr. Davies: Would you care to speculate why birth seems to switch the control of growth from one largely autocrine and paracrine to one more endocrine? In those infants who are born very prematurely, does this switch take place at the same time? Is this simply part of a maturational march, or is there another reason for the switch?

Dr. Rappaport: Even when a child is born prematurely, TSH and thyroid function mature in the first 24 hr, as they would in a child who is born at term. There is a switch. Most people working in developmental biology are looking for a change in the genetic expression at the time of birth, just before, or just after, explaining why some signals appear all of a sudden at birth. For instance, there are two growth factors: somatomedin-C, or IGF I and IGF II. The IGF II is more important for fetal growth; it has been demonstrated in the rat that IGF II decreases after birth, when it probably becomes less important than IGF I, which is totally GH dependent. Thus, the GH dependence of growth that occurs at birth goes along with a rapid increase of IGF I. Although these data cannot be transferred to the human yet, they give some information about possible changes in the genetic expression for the synthesis of these growth factors that could explain how the body at the time of birth comes under the control of GH, which prior to birth is of no importance. Dr. Milner, would you like to comment further on this?

Dr. Milner: I think the switch is related to parturition, in particular, to the switch to enteric nutrition as opposed to intravenous nutrition via the umbilical cord, and to the removal of placental lactogen. Everything else you said I agree with.

Dr. Kraisid: Has any relationship between the level of physical activity or exercise and growth factors been documented? Since changes in growth velocity are observed during various seasons when children could increase or decrease their physical activity, is there any evidence that hormonal changes also occur during periods of increased activity?

Dr. Rappaport: I am not very familiar with the relationship between hormones and physical activity. Here again, we always look at very extreme models. Athletes are one of the extreme models of intensive physical activity. These people are probably in a very special situation: they present with something like a nutrient deficiency because they behave very much like anorexia nervosa patients and on top of it have a strenuous physical activity. As a result, they frequently grow less than normal, puberty is delayed, and they sometimes end up shorter. However, I have no data on regular physical activity in undernourished populations; it might be a totally different situation.

REFERENCES

