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CAUSES WHICH LIMIT THE GROWTH OF THE ANIMAL BODY

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Abstract: *My title is a translation of that of the very first scientific study of human growth* (Causas incrementum corporis animalis limitantes) *which was made by Christian Friedrich Jampert in 1754 on children of the Berlin Royal Orphanage. I examine the question: in what sense do we know more now about factors responsible for the variation in height in a population than did Jampert. I discuss growth regulation and catch-up; the growth curves of tall and short adults; the mechanism of the growth plate; and the reasons why variation in growth hormone level are not responsible for adult height variation. More likely candidates are variation in the amount of IGFI secreted by the proliferative cells of the growth plate, variation in the IGFI receptors, or variation in the control of the number of divisions the cells make before exiting the cell cycle.*

Key words: *Christian Friedrich Jampert; Genetic–environment interaction; Catch-up growth; Growth plate; Growth hormone.*

Introduction

The title of my paper "The causes which limit (or perhaps better, control) the growth of the animal body" is a quotation from the 18th century. It is the title of the doctoral thesis ("Causas incrementum corporis animalis limitantes") in which appeared the very first study of human growth, a study made in the Spring of 1754 by Christian Friedrich Jampert on children of the Berlin Royal Orphanage. It was defended on October 5th 1754 in the medical school of Halle, a small town a little to the north of Leipzig, which at that time was one of the great centres of European scholarship and particularly medicine. I chose the title first because it describes exactly the subject I am going to discuss and second because Jampert is something of a favourite of mine. Chiefly, this is because he was the first person ever to publish measurements of children at successive ages (he measured just one boy and one girl at each year of age, choosing each time one he thought typical of the age group). But also, I confess, it is because I myself resurrected him from a totally undeserved oblivion. He had a brilliant but hopelessly short career, dying, probably of tuberculosis, just four years after he graduated. He emerged, like Lazarus, when I was turning over the gravestones of the British Museum Library in the late 1970's. All the other 18th century theses on growth were boring, repetitive, barbarously written and lacking any observational data whatever. Jampert's, in total contrast, was alive, modernly scientific in outlook and analysis, and written with elegance and understanding (Tanner, 1981; Tanner, 1989a).

Jampert's view of what limited the growth of the animal body was iatro-physical, in the new scientific-mechanical tradition of the Italians Borelli and Bellini – derived from Galileo – in which the hydraulics of body fluids were given a prominent place in physiology and medicine. Growth results from the pressure of the fluids in the blood vessels being greater than the resistance of the fibres of the body, especially those of the bones. The body therefore stretches and this ceases when the ever-increasing resistance finally equals the fluid pressure. Girls grow up earlier than boys because their fibres have less resistance, so stretch more easily. At least this is true of girls in comfortable

circumstances. Working girls, whose fibres are toughened by their toil, grow up scarcely any earlier than boys, and rarely menstruate before 17 or even 20 years of age.

The question I should therefore like to address is: can we do any better than Jampert at explaining the causes that limit growth? How do we see the problem nowadays? It is convenient to start by distinguishing what Aristotle would have called 'final' and 'efficient' causes; in other words, results themselves and the mechanisms by which they are achieved. First then, the phenomenology of the regulation of growth; later, a discussion of how the regulation is effected.

Phenomenology: Genetic–environment interaction and catch-up growth

It is a truism that the ultimate stature attained by any individual is the result of the continuous interaction, throughout the whole growth process, between forces set in motion by the genes and the effects of the environment. The interaction is not necessarily additive, nor constant from age to age. There are some periods of growth more sensitive than others to environmental deprivation, and there are some individuals who are more able to resist a bad environment than others, so that two children who might have grown up to be identical in height in an optimal environment may well have different heights in a suboptimal one.

But the childhood organism has an astonishing capacity for recovery from environmental set-backs unless they are severe and prolonged. In the individual the process is known as catch-up growth (Prader, Tanner and von Harnack, 1963) because the child whose growth has been slowed by malnutrition perhaps, or a hormone deficiency, resumes growth at a greater-than-normal velocity when food or the hormone is supplied again and thus catches up in height to or at least towards the height he would have been in the absence of the growth restriction. In other words, he seeks to regain his pre-programmed growth curve. When he gets to it, he throttles down, and goes along it once again as though nothing had happened. *Figure 1* shows an example of the process.

A particularly interesting example of catch-up demonstrated by a whole population occurred in Holland during the last stages of World War II. Between October 1944 and May 1945, there was a severe famine in the central part of Holland, including in Rotterdam. In the cohort of children exposed to the famine during their last three months *in utero*, birthweight diminished by 9% and birth length by 2.5%. At age 19 the males of this cohort entered military service; their heights and weights by that time were no different from those of their contemporaries who had not been undernourished (Stein et al. 1989). Even from such an extensive and such an early deficit, catch-up can be complete provided the undernutrition does not last too long and provided that conditions are genuinely good during the rest of childhood.

Our current picture of the environmentally-caused stunting that occurs in a large proportion of the population of the Third World is as follows. Birthweight is often little below that of the developed countries, and length and weight growth is normal during the first six to nine months after birth. Thereafter recurrent infections interact with a nutritional intake already at borderline level. During an episode of infection, nutritional intake falls, and growth slows down or stops. When the infective episode finishes, catch-

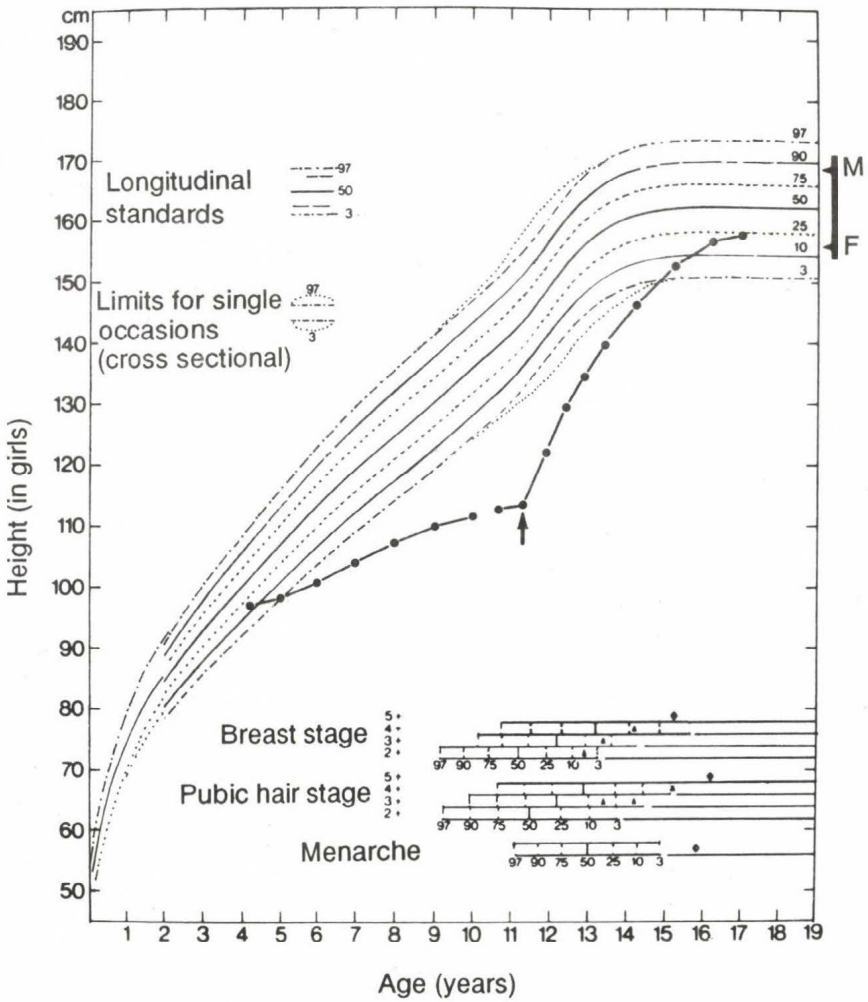

Fig. 1: Growth in height of a girl with coeliac syndrome to show catch-up on commencement of diet (marked by an arrow). From Tanner (unpublished)

-up growth restores the situation to normal in a child easily provided with the extra calories necessary to fuel it. But the amount of calories is considerable, and in the Third World these are often unavailable. Thus repeated infections, particularly during the age period of nine months to about five years, result in a lower adult height than the genes had planned for. Precisely the same mechanism seems to be at work in generating the (much smaller) differences seen between social classes in most countries of the industrialised world. Here also most of the adult differences, typically around 3 cm between non-manual and unskilled manual classes, are established in the age period nine months to three years (see Tanner, 1989b, pp 133; 149).

So much, albeit briefly, for the environmental effects limiting adult height. We now turn to the *genetic* ones, supposing we have a population all growing up in comfortable, middleclass circumstances, with loving, intelligent – even Green – parents. In passing we have to remember that the mechanisms controlling catch-up in the *individual* may be quite different from the mechanisms controlling variation *between* individuals growing up in circumstances where catch-up is unnecessary. The standard deviation of adult height in such a well-circumstanced population is about 6.5 cm in men and 6.0 cm in women. The range of heights which includes 95% of such men is thus about 26 cm. But the range of heights amongst brothers is a great deal less than this; in fact about 16 cm. And the range amongst monozygotic twins, in these circumstances, is only 1.6 cm, of which at least half must represent the inevitable measuring error (see Eveleth and Tanner, 1990).

Table 1. **Mean difference between lengths of monozygotic twin pairs (140 pairs) and same-sex dizygotic twin pairs (90 pairs) from birth to 4 years, and within-pair correlation coefficients [From Wilson (1979), cited in Tanner (1989b)]**

Age	Mean difference in length (cm)		Correlation coefficient	
	MZ pairs	DZ pairs	MZ pairs	DZ pairs
Birth	1.8	1.6	0.58	0.82
3 months	1.4	1.6	0.75	0.72
6 months	1.3	1.9	0.78	0.65
1 year	1.3	1.8	0.85	0.69
2 years	1.1	2.4	0.89	0.58
3 years	1.1	2.9	0.92	0.55
4 years	1.1	3.2	0.94	0.60

This genetic control is a highly active regulatory force. Monozygotic twins have to work at reaching the same ultimate height; they do not start out that way. *Table 1* (from Wilson, 1979, cited in Tanner, 1989) shows the well-known values from Wilson's superb study of twins in Louisville, Kentucky. At birth MZ pairs showed just as much difference in lengths as DZ pairs, this because birth length depends so much on the precise position, blood supply and so forth, in the maternal uterus. By three months the MZ twins' difference had diminished from 1.8 cm to an average of 1.4 cm; and by two years it was down to 1.1 cm where it stayed till four years. DZ pairs, in contrast, increased their between-pair differences, from 1.6 cm at birth to 2.4 cm at two years and 3.2 cm at four years.

Thus, in summary of the phenomenology, we can say that final adult height is controlled by the genes, provided the environment is sufficiently favourable to permit them to carry out their plans. Thus the differences amongst a set of five brothers growing up in optimal circumstances measures their genetic difference. The difference between the *mean* of their heights and the *mean* of the heights of five other brothers of the same ethnic group but growing up under deprived circumstances measures the effects and the depth of the deprivation.

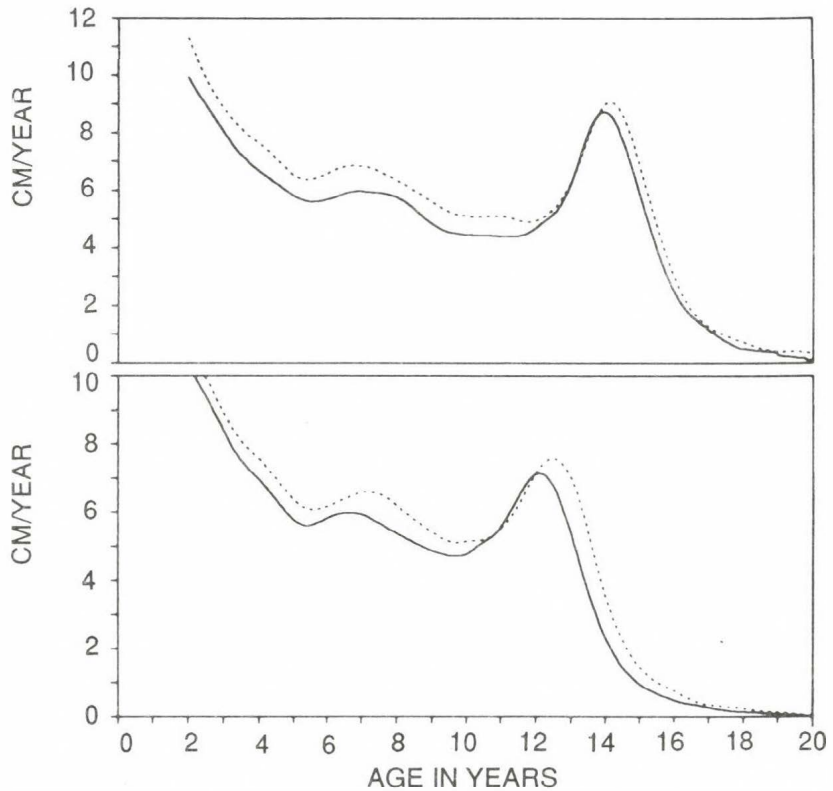

Fig. 2: Growth velocity structural average curves of tall and short children of Zurich First Longitudinal Study (from Gasser et al. 1989)

One last point of phenomenology before we pass to mechanism: At what point during growth does the difference between tall and short adults chiefly arise? Surprisingly it is only very recently that this question has been addressed by researchers working on the major longitudinal studies of growth around the world. Gasser and his associates (1989) have contrasted the growth curves of the 25% tallest (as adults) and 25% shortest boys and girls of the Zurich First Longitudinal Growth Study. They used a particularly sophisticated method to produce the "structural" average curves shown in *Figure 2.* It can be seen that most of the difference arises from the tall having a consistently greater growth velocity between the ages of two and the beginning of puberty. Before two and during puberty, the differences in the velocity curves are less.

In these data in fact, about 80% of the difference between tall and short has arisen before puberty; only about 20% is contributed by a greater pubertal spurt in the tall. Another way to look at these figures is by calculating the ratios of the heights of the short and tall at successive ages. At two years the ratio is little less than unity; at maturity it is 0.92 for both girls and boys. It thus decreases during growth. At the beginning of puberty it has already reached 0.93 in the boys and 0.92 in the girls.

Incidentally, the age at which peak height velocity is reached is about 0.3 years later in the tall, of both sexes, than in the short. This is a small difference, amounting to 0.3 SD of age at PHV, but it is a statistically significant one.

Thus when we consider mechanisms we will want in particular to concentrate on factors regulating velocity during the period from age two to the beginning of puberty.

Mechanisms: the growth plate, hormones and genes

We now discuss the mechanisms by which regulation and limitation of adult stature are effected. Let us start at the peripheral end of the chain and work gradually backwards.

Since in Man the great majority of growth occurs postnatally and we are in any case concentrating on the period of prepubertal childhood it is the physiology of the epiphyseal growth plates that is our prime interest. In the typical plate there is next to the epiphysis a layer of stem cells (very narrow in most mammals, but surprisingly wide in Primates, for reasons unknown). Above this is the proliferative chondrocyte zone, then the zone of hypertrophied chondrocytes, ending at the point where the cartilage plate gives way to the metaphyseal bone (*Fig. 3*). Seen from above the growth plate is a relatively thin, disc-like structure, a sort of washer between epiphysis and metaphysis.

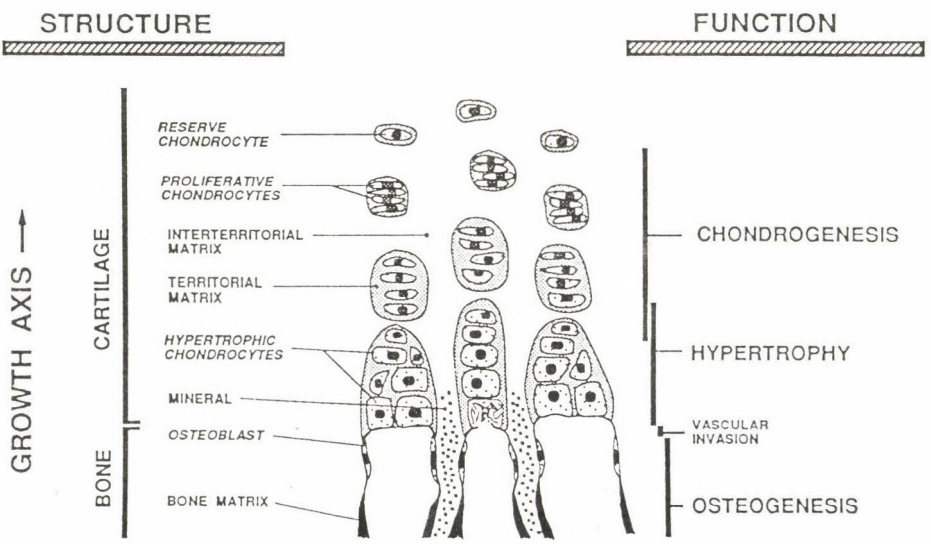

Fig. 3: Diagram of growth plate: Structure–function relationships (from Horton, personal communication)

Seen from the side, it consists of several thousand axial columns, each separated from the others by longitudinal septa, which constitute the intercolumnar matrix. At the bottom of each column lies a single stem cell, or prechondrocyte, which is the origin of all the cells making up that particular column. Stem cells have a low frequency of

division; proliferative cells divide more frequently, but exhaust their mitotic ability after six to eight divisions. They then turn into the massive hypertrophic cells, which continue to secrete a succession of substances, finally dying and being removed by the encroaching metaphyseal bone front. In the distal femoral epiphysis, the only extensively studied growth plate in Man, there are about 35 proliferative and seven hypertrophic cells in a column at any given moment during the childhood years (Kember and Sissons, 1976). All of these cells constitute a clone of the original stem cell. Eventually all the members of the clone terminate their life cycles by being engulfed by the advancing metaphyseal bone, but meanwhile a stem cell neighbour has divided and given rise to a new clone, opening up a nearby parallel channel (or even perhaps using the same channel). Kember and Sissons estimated that to grow a rat's tibia would require some 40 or so stem cell divisions, that is 40 successive clones. Calculations indicate that the clone size in the human femoral growth plate totals around 200 cells (compared to the rat's 60) a figure which implies that a large number of stem cell divisions must also occur during human growth.

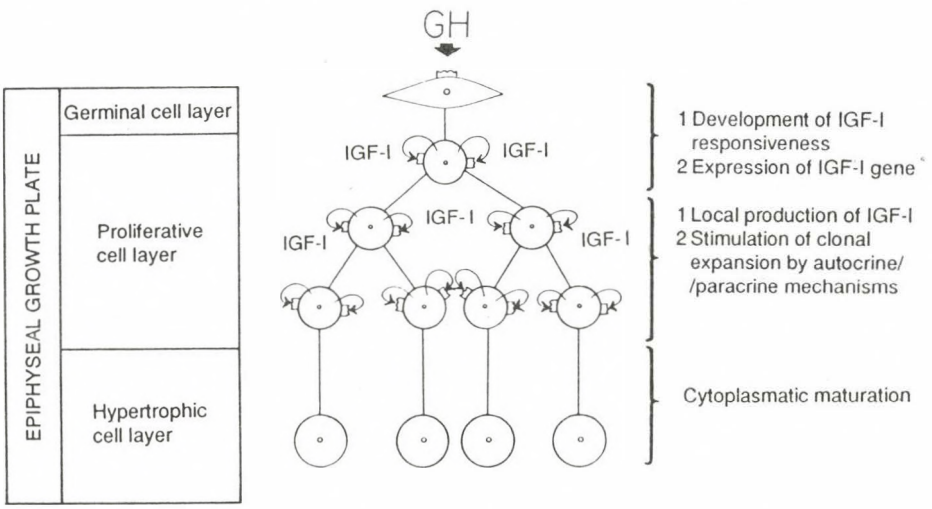

Fig. 4: Diagram of physiology of the growth plate (from Isaksson et al. 1987)

The modern picture of the physiology of the growth plate owes much to the studies of Olle Isaksson and his colleagues in Gothenberg (1987). As indicated in the diagram of *Figure 4*. growth hormone acts solely or mainly on the stem cells, stimulating them to divide in a characteristic asymmetrical division, one daughter cell differentiating into a first generation proliferative cell, the other remaining as a stem cell. Differentiation involves a change of phenotype, with the appearance of a range of structural proteins, and an activation of the genes expressing a number of factors, amongst which is the all-important IGF I and also its membrane receptor (the little square in the Figure). IGF I, a 70-amino acid peptide, stimulates division of the proliferative cells by autocrine and paracrine actions. After some six to eight divisions (on average) the proliferative cells

run out of the capacity to divide further, or, as the cell biologists put it, are withdrawn from the mitotic cycle. The molecular biology of this all-important event is not understood.

Growth hormone is therefore an important control for longterm post-natal growth, causing replacing of the clones every few months in the human (and every week or so in the rat). (Children totally lacking growth hormone due to a gene deletion do grow but end some 6 SDs below normal: as usual therefore it seems that the growth hormone acts as catalyst to speed up a process which, in a small way, takes place without it.) IGF I controls shorter-term growth. The whole process is very highly regulated, so that production of chondrocytes at one end of the column and destruction at the other remain in a fine-tuned balance. The regulation almost certainly involves feed-back from the cartilage matrix to the cell columns, and it is likely that small molecules diffuse down from the metaphyseal bone front into the hypertrophic layer, the end-point of their diffusion perhaps being one of the factors marking the proliferative-hypertrophic border.

Turning to the *rate of growth:* the total amount of growth achieved in a given time by a growth plate column depends first on the number of new proliferative cells added in that time (each one contributing some 9 microns); secondly, on the increase in height of each chondrocyte when it changes from proliferative to hypertrophic (about 24 microns added) and thirdly on the amount of matrix synthesised and lodged within the structure of the column (mainly between the cells of the hypertrophic zone). The first factor, the number of proliferatives added, itself depends on two things: the number in the column open to division, and the average frequency with which they divide, the so-called cell cycle time.

The cell cycle time has been worked out only for one growth plate in Man, that of the *distal femoral epiphysis.* In the early days of the Harpenden Growth Study (Tanner, 1962) lateral radiographs of the knee were taken at six monthly intervals and in about a quarter of the plates we could see the transverse lines of growth known as Harris' lines. These persist for several years and hence can be used as markers in exactly the same way as layers of injected tetracycline are used in experimental animals. Thus the growth rate at the epiphysis can be calculated, and since the size of the hypertrophic cell is known, the number of hypertrophics eliminated per unit of time is calculable. It turns out that the cell cycle time in this human growth plate during mid-childhood is around 20 days, which contrasts with the cell cycle time in the rat tibial epiphysis which is 2.5 days.

Age Factors

It seems that the diminution of rate of growth which occurs as the child or young animal gets older is due to a progressive decrease of cell production in the proliferative layer. In the rat tibial epiphysis for example, the rate falls from about 11 cells/day at its maximum to 8 cells/day at 40 days and 4 cells/day at 80 days (Hunziker and Schenk, 1989; Thorngren and Hansson, 1973). The cell cycle time remains unchanged, so an increasing proportion of cells seems to be withdrawn from the cycle. Since it is local IGF I which stimulates cell division this may imply that local IGF I levels diminish with

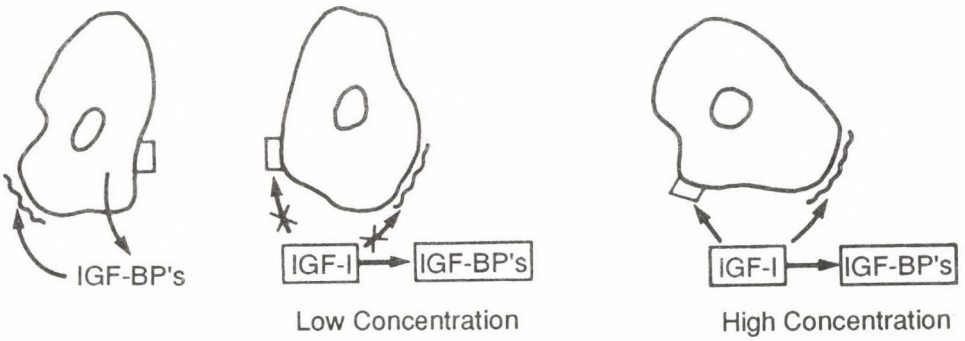

Fig. 5: Illustration of action of IGF I binding proteins (from Clemmons, 1990)

age. Alternatively the amount of IGF I receptors on the cells may decrease as the cells get "older" either in a chronological sense, or in the sense of being products of an increasing number of cell divisions. A third possibility concerns the recently recognised interaction with IGF I binding proteins. There are several such in the extracellular fluid matrix surrounding the cartilage cell, and at low concentrations of IGF I they sop up, as it were, most of the IGF I secreted so that none is left to couple with the cell receptor. At higher concentrations, when these BPs are relatively saturated, IGF associates with its receptor (the rectangle in *Figure 5*) and another class of binding proteins, this time associated with the cell surface (the wavy lines). Thus alterations in the tissue matrix along the growth column, long suspected to exist on other grounds, could so regulate things that at the bottom of the column much IGF I went to the receptor, but further up less and less. Similarly, as the animal aged the binding power of the matrix may increase, so diminishing the production rate of proliferative cells. This represents the limit of our knowledge at present, but the field is a very active one (see Clemmons, 1990; Sara and Hall, 1990).

Morphological Factors

The differences between rates of growth at different epiphyses, in contrast, depend on the total number of proliferative cells in the columns of the growth plate. Thus a species with long arms and short legs would have longer proliferative zones in the arms than an oppositely proportioned species. Longer zones imply greater cell proliferation for the same cycle time, simply because of the number of cells available. What controls the length of the zones is unclear, but it must be a local property of the clones. Thus as overall growth velocity slows due to a general withdrawal of cells from the mitotic cycle, body proportions are maintained, the percent of cells withdrawn being in general the same at each growth plate (though there are exceptions implying reversal of growth gradients, particularly at puberty, perhaps due to differential loss of stem cells rather than proliferatives).

Effect of Growth Hormone

So, finally, what is it that determines the slightly higher childhood velocity which distinguishes the tall from the short? The amount of growth hormone secreted is a possible candidate, and there are some paediatric endocrinologists who indeed believe this is the mechanism. Their evidence, however, is for the most part derived from single 24-hour GH profiles on very small, i.e. less-than-2 SD-for-height children contrasted with very tall, more-than-2SD-for-height, and it is hazardous to intrapolate the same mechanisms to explain the variability seen amongst the more usual members of the population.

It is certainly true that administering extra growth hormone to children who are "small small" (i.e. less-than-2SD), *probably* including those who are so for perfectly respectable genetic reasons, does result in a small increase of height velocity for at least three or four years – perhaps more, we do not yet know – and the increase is of the general order of the difference shown between tall and short in *Figure 2*. Whether this treatment results in an ultimate height gain – of any sort, let alone the 16 cm differentiating tall and short – is questionable. We have to note, too, that other paediatric endocrinologists attribute differences in *tempo* of growth to differences in secretion rates of growth hormone. Since tempo is unrelated to final height, both sets of endocrinologists cannot be right. But both could easily be wrong.

The physiological control of GH secretion is complex and depends on an interaction between somatostatin and GHRH secretion. The feedback systems fixing the levels are incompletely understood. If levels of GH were to be the basis of this mechanism, it would presumably imply a slightly greater rate of clonal replacement in the tall, a sort of pressure from the bottom upwards on the growth plate.

There is, however, a powerful argument against GH level accounting for more than a small proportion of the genetic influence on adult height. If a polygenic system for control of GH secretion were the only genetic system concerned, then when its outcome was blocked – in growth hormone deficiency due to failure of cells downstream of the genetic mechanism – both variance and mean in such a population would be drastically reduced. Furthermore the covariance with the parents' height would also tend to zero. In practice, neither of these things happens. In one of the largest series of such patients (Burns et al. 1981) the variance of height for age was virtually normal at diagnosis (i.e. before treatment) as well as at adulthood. And the correlation with midparent height was also the same as in normals both at diagnosis and finally. At diagnosis the value was 0.55 for 39 cases, of which 26 were prepubertal and of average age about 11.5 years, and 13 cases in early puberty, which would lower the correlation a little, as it does in normals. At maturity the value for the whole group was 0.72. At the most, therefore, genes controlling the secretion level of GH play only a small part amongst the perhaps numerous polygenic systems controlling adult height.

Genetic Control

Another direction in which to look for the mechanisms that control growth would be in factors which control the expression of the gene for IGF I which is located on the long arm of chromosome 12 and has five exons which transcribe alternatively to produce two

mRNA's encoding two different IGF I precursor proteins. This may provide a mechanism for variation in IGF I biological activity. Then there are the factors which control the gene for the IGF I receptor, a gene located on chromosome 15.

A further suggestion concerning the greater velocity of the tall is the straightforward one that the lengths of their proliferative zones are just a little greater than in the short. This implies that the factors fixing the line of proliferative-hypertrophic demarcation differ quantitatively. Kember (1979) has made a number of suggestions on how this line may be determined, but nothing certain is known about the mechanism. It seems to me likely that so precise a demarcation is more likely to result from a push-pull mechanism than simply a push on its own. By this I mean that an interaction of small molecules defusing downwards from the metaphysis with small molecules, perhaps IGF I itself, diffusing upwards from the proliferative layer would seem to be more stable, and more open to small genetically-controlled differences, than just the mechanism which Kember suggests, of upward diffusion only.

Of the genetic differences between tall and short that control these mechanisms, we know very little. We presume that height is controlled by a fairly large number of genes, each having a relatively small effect. Most or all of these are on the autosomes, though we do not know where. There have been suggestions that at least one fairly major gene may be located on the X chromosome (Goldman et al. 1982; Eiholzer et al. 1988) but the pattern of familial correlations is against this (Mueller, 1986), as is also the finding that the parent-offspring correlations for height remain entirely unaltered in XO Turners syndrome (Massa et al. 1990). Using the same argument as in the case of growth hormone deficiency above, this preserved correlation means that at most only a small proportion of stature-controlling genes can be on the X chromosome.

Conclusions

And so we return to Christian Friedrich Jampert and the question we set out to answer: can we do any better at explaining the causes which limit growth than his hydraulic theories of the 18th century? Well, I suppose we can; at least we can do *more*. And we can surely agree with the way he ends his thesis. Growth, he says, is not determined in an exact fashion at a given age, but varies according to circumstances. "Growth is effected," he writes in italics "by the conjunction simultaneously of many causes . . . and to enumerate all these, explain them and indicate their applications to individuals is scarcely the work of one man only, much less the theme of a modest dissertation".

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