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FETUS into MAN

Physical Growth from Conception to Maturity

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Introduction

This is a book which describes the process of growth in children in terms which I hope the biologically unsophisticated reader will understand and the biologically sophisticated approve. Where complexity exists, I have said so plainly, avoiding, I hope, all facile generalizations. I have sometimes entered into details, but only when they are elegant, instructive and undisputed. Biology is like a Van Eyck painting; as you approach closer, clarity actually increases. The focus holds true down to the tiniest detail. The clothes of the street vendor seen in the far distance through the window are as clear, under the magnifying-glass, as the robes of the foreground personages talking in the room. Such perspective is not of the eye but of the mind; and I must beg the reader to use an equal facility of focus as we traverse between broad and narrow views.

Though a little biological knowledge on the reader's part is certainly helpful, I have not assumed it. Chromosomes, endocrines, proteins, codons, centiles and regressions are all explained as we go along. I have, however, assumed that readers know the names of parts of the body, including those of which they have no personal experience.

Chapter 1 presents the phenomenon we are going to study, the curve of growth of the child. It is the curve of height that is given; this is the characteristic we single out in everyday speech, for we talk of a child 'growing up'. But at the outset one must realize that growth is far from being a simple and uniform process of becoming taller or larger. As the child gets bigger there are changes in shape and in body composition and in the distribution of various tissues. In the newborn the head represents about a quarter of the total length; in the adult about one-seventh. In the newborn much of the muscle still consists of water; in the three-year-old the muscle cells are packed with contractile protein. Different tissues (such as muscles, nerves, liver) mature at different rates and the growth of a child consists of a highly complex series of changes. It is like the weaving of a cloth whose design never repeats itself. The underlying threads, each coming from its reel at its own rhythm, interact with one another continuously, in a manner always highly regulated and controlled.

The fundamental biological questions of growth relate to these processes of regulation, to the programme that controls the loom. At present very little about this is understood. In Chapter 2 we discuss cells, the fundamental units of growth, and distinguish between organs such as the skin, where cells are continuously produced to replace those that continuously die, and organs such as the nerves and muscles where cells, once formed, remain throughout most of the animal's life, and no new cells can be formed once the growth period is over. There is too little certainty about the way that cell and organ growth is regulated for a long consideration of this to be included, but in Chapter 10 we return to consider the regulation of growth in the whole organism, after we have accumulated sufficient knowledge to make some sense of it. Perhaps it is worth saying to the non-biologist reader that if Chapter 2 proves difficult for him, which I hope it will not, he can take courage from the fact that all the rest is easier.

In Chapter 3, prenatal growth is described. Perhaps the most surprising fact that has emerged in the last few years is how many fertilized ova fail to result in a live baby. About 50% of all conceptuses are spontaneously aborted, nearly all because of intrinsic faults in their make-up. We have to adjust ourselves to the notion that children with certain diseases such as Down's syndrome (or mongolism) and Turner's syndrome are the rare survivors from cohorts nearly all of whose members die in the first few weeks after conception.

In Chapter 4, the chromosomal and endocrine control of sex differentiation in utero and in early childhood is described, and in Chapter 5 the further differentiation that takes place at puberty. The last two decades have seen a great increase in our understanding both of the bodily changes of puberty (and especially of their great variability), and of the endocrine mechanisms which control them. The whole subject of childhood and pubertal endocrinology is at last beginning to make sense, owing chiefly to our growing ability to measure very small amounts of hormones by chemical or biological means. Further advances will now depend increasingly on studies of normal adolescents followed individually all through puberty, and that demands another and perhaps more difficult skill than the manipulation of chemical assays.

Different children experience puberty at very different ages, so that amongst a group of twelve-year-old girls or fourteen-year-old boys there will be some who have not yet started their pubertal changes and others who have practically finished them. This variability, which is almost entirely biological in origin, has important social and educational consequences. Though seen most clearly at puberty, the differences in tempo of growth – whether the course of growth is played out quickly or slowly – are present at all ages. The concept of physiological maturity, or developmental age, has thus arisen, and Chapter 6 is devoted to its description, measurement and implications.

In Chapters 7 and 8 two of the most important organ systems have been singled out: the endocrine glands because they play such an overwhelmingly important part in the control of growth and sex development, and the brain because it is of such interest and importance to human beings. Our increased understanding of endocrine events has enabled one particularly spectacular advance in medicine to be made. Some children – mostly boys – grow up to be very small, though of quite normal proportions, because they lack the growth hormone normally secreted by the pituitary gland. Normal growth is restored by injection of the growth hormone (just as injections of insulin restore the metabolic situation of diabetics). Only growth hormone from humans works, however, so it has to be obtained from human pituitaries after death. This is now done on a large scale in many countries, and these children if diagnosed early enough can look forward to becoming perfectly normal-sized

No such spectacular advance has taken place regarding brain development. However, there is now quite a large number of research workers throughout the world devoting themselves to this technically very difficult field, and it seems safe to predict that in the next ten years we shall have achieved real knowledge about how the complex structure of the brain is generated during growth and even about the ways memories are stored. Already the work of Hubel and Wiesel and their many followers, described in Chapter 8, shows how the visual system, including the cells of the cerebral cortex, depends for its development on a precise interaction between the environment and the nerve cells. This interaction has to occur at a particular time, known as a 'sensitive period', in the animal's maturational calendar. (Sensitive periods pervade the whole of growth, as the reader will soon discover.)

Chapter 9 is a long one. It discusses the effects of the interaction of genes and environment on growth. Differences in growth between one family and another, and between one population group and another, are detailed; the effects of undernutrition are described, and of factors associated with social class, numbers of brothers and sisters, climate, psychological stress, illness and urbanization. In this field also things are rapidly becoming clearer. We are beginning to have examples of populations of all the major racial groups living under similar environmental circumstances. For example, in the U.S.A. persons of European and of African origin growing up under similar circumstances have very similar growth curves for height though not for body proportions. Under similar conditions Asians from Japan and China seem to be a little smaller and to mature a little faster. Throughout the industrialized world there has been a tendency during the last hundred years for children to become larger and reach maturity earlier, a tendency now reaching its end. Though rate of growth remains one of the most useful of all indices of public health and economic well-being in developing and heterogeneously developed countries, it must not be thought that bigger, or faster, is necessarily better. From an ecological point of view smallness has advantages; here also a change of attitude has recently been developing, with simplicity giving way to a more sophisticated search for balance.

In Chapters 11 and 12 standards for normal growth are given and some of the common pathologies of growth are briefly described. The standards provide a do-it-yourself health visitor's kit for parents interested in seeing how their children grow (comparing children's growth curves by marks made on a door specially designated for this purpose was a common pastime in large Victorian families). The proper method of measuring length or height (all too seldom followed by the health professionals) is described; how to plot the results on a chart; and how, at certain ages, to see if the child takes after the parents. Tables for predicting the probable adult height are also given. In all these standards there is very great normal variation and readers must be warned to read exactly and with caution. A famous statistician once observed that, unfortunately, there was no way of preventing half the people being below the average. Similarly, 3% of perfectly normal children are below the line on the chart called the 3rd centile, which is often taken as the arbitrary limit of normality. However, if a child is far below the standards then certainly the cause for this ought to be sought, particularly nowadays when growth-hormone deficiency, at least, can be successfully treated.

Finally, as to further reading: it seemed wiser in general not to put references in the text, where the general reader may find them distracting. I have provided instead a two-tiered bibliography for each chapter, consisting of a short list of further reading in which each paper is annotated, and a longer list of references without annotations. Where authors' names are mentioned in the text the relevant papers will be found listed in the References.

Very many colleagues and friends have helped by criticizing early drafts. I am especially grateful for the comments of Bryan Senior, Vreli Fry, Marjorie Baines and Kenneth Sass, who undertook the arduous task of reducing to a minimum the number of paragraphs incomprehensible or boring to the non-biologist. Messrs R. H. Whitehouse and Noel Cameron, and Professor Jim Garlick and his students at Cambridge, served as human biologist assessors, and Dr Michael Preece, Dr B. A. Tanner and Professor W. A. Marshall as clinical scrutineers. The faults that remain are mine. Lastly, I wish to thank Ray Lunnon and Brian Kesterton for the pictures and diagrams, Jan Baines for assembling the material and dissembling, at times, my presence in the office, and Sara Dunford for her cheerfulness and care over innumerable typescripts.

J. M. Tanner
Institute of Child Health, London, July 1977

CHAPTER 1

The Curve of Growth

Figure 1 shows the most famous of all records of human growth. It concerns the height of a single boy, measured every 6 months from birth to 18 years. This is the oldest longitudinal record in existence, and it remains, for our purpose of illustration, one of the best. It was made during the years 1759–77 by Count Philibert Guéneau de Montbeillard on his son and it was published by Buffon in a supplement to the *Histoire Naturelle*.

In Figure 1a is plotted the height attained at successive ages; in 1b the increments in height from one age to the next, expressed as the rate of growth per year. If we think of growth as a form of motion (analogous to the journey of a train) then the upper curve is one of distance travelled; the lower curve, one of velocity. The velocity, or rate of growth, naturally reflects the child's state at any particular time better than does the distance achieved, which depends largely on how much the child has grown in all the preceding years. Thus, for those substances which change in amount with age, the concentrations in blood and tissues are more likely to run parallel to the velocity than to the distance curve. Indeed, in some circumstances it is the acceleration rather than the velocity curve which best reflects physiological events.

Figure 1b shows that in general the velocity of growth decreases from birth (and actually from about the fourth month of foetal life; see Chapter 3), but that this decrease is interrupted shortly before the end of the growth period. At this time, from 13 to 15 years in this particular boy, there is a marked acceleration of growth, called the adolescent growth spurt. (Some writers distinguish sharply the terms 'adolescence' and 'puberty' though not all who do so agree in their distinctions. Some use puberty to refer to physical changes, adolescence to refer to psychosocial ones. I have used the terms interchangeably in this book.) From birth until age 4 or 5 the rate of growth in height declines rapidly, and then the decline, or deceleration, gets gradually less, so that in some children the velocity is practically constant from 5 or 6 up to the beginning of the adolescent spurt. A slight increase in velocity is sometimes said to occur between about 6 and 8 years, providing a second wave on

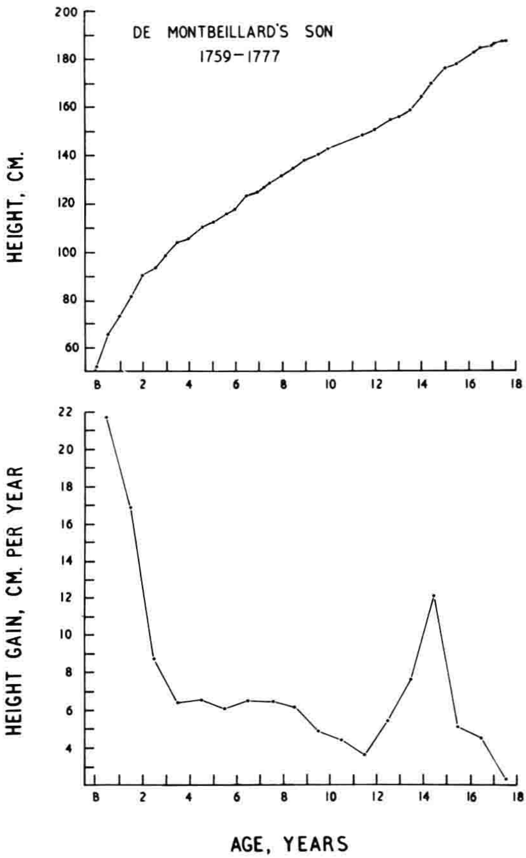

FIG. 1. Growth in height of de Montbeillard's son from birth to 18 years (1759–77): (*above*) distance curve, height attained at each age; (*below*) velocity curve, increments in height from year to year (From Tanner, 1962, drawn from data of Scammon, 1927)

the general velocity curve. Although Figure 1 seems to show its presence, examination of many other individual records from ages 3 to 13 fails to reveal it in the great majority; if it occurs at all, it is in a minority of children.

Growth is in general a very regular process. Contrary to opinions still sometimes met, growth in height does not proceed by stops and starts, nor does growth in upward dimensions alternate with growth in transverse or, more ominously, anteroposterior ones. The more carefully the measurements are taken, with precautions, for example, to minimize the decrease in height that occurs during the

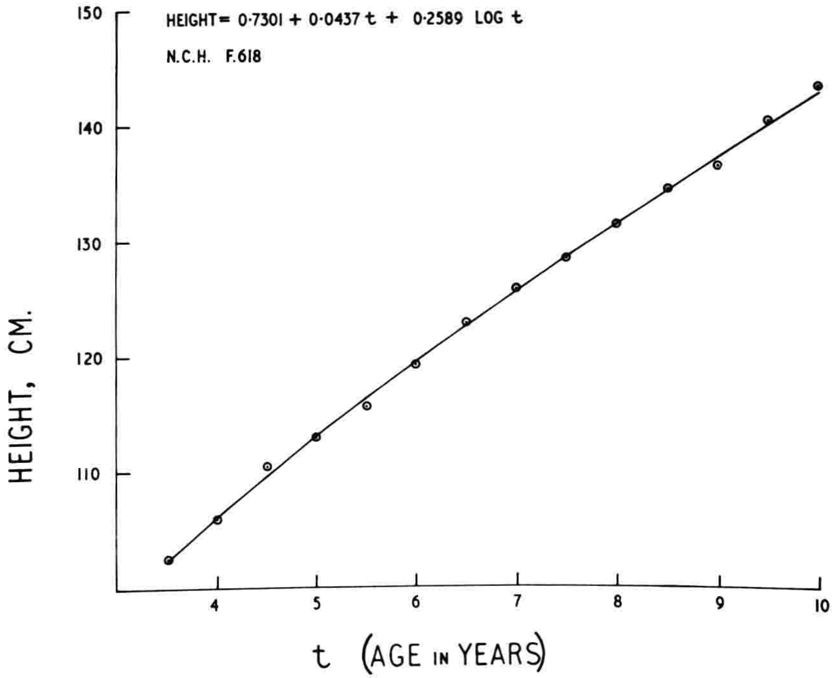

FIG. 2. Curve of form $y = a + bt + c \log t$ fitted to stature measurements taken every 6 months by R. H. Whitehouse on a girl from ages 3·5 to 10·0 years
(Harpenden Growth Study)
(From Israelsohn, 1960)

day for postural reasons, the more regular does the succession of points in the graph become. Figure 2 shows the fit of a smooth mathematical curve to a series of measurements taken on a child by the same observer, my colleague R. H. Whitehouse, every 6 months from ages 3·5 to 10·0. None of the points deviates from the line by an amount more than measuring-error. This is generally true, although in some children regular seasonal variations (discussed in Chapter 9) superimpose an added 6-month rhythm about the curve. There is no evidence for 'stages' of growth in height (or any other physical measurement) except for the spurt associated with adolescence. Perhaps increments of growth at the cellular level are discontinuous; but at the level of bodily measurements, even of single bones measured by x-rays, we can only discern complete continuity, with a velocity that changes gradually from one age to the next.

Many attempts have been made to find mathematical curves which fit, and thus summarize, human and animal growth data. Most have ended in disillusion or fantasy; disillusion because fresh data failed to conform to them, fantasy because the system eventually contained so many parameters (or 'constants') that it became impossible to interpret them biologically. What is needed is a curve or curves with relatively few constants, each capable of being interpreted in a biologically meaningful way; yet the fit to actual data must be adequate, within the limits of measuring-error. Part of the difficulty arises because the measurements usually taken are themselves biologically complex. Stature, for example, consists of leg length, trunk length and head height, all of which have rather different growth curves. Even with such relatively homogeneous measurements as forearm length or calf–muscle width, it is not clear what purely biological assumptions should be made as the basis for the form of the curve. The assumption that cells are continuously dividing leads to a different formulation from the assumption that cells are adding constant amounts of non-dividing material, or adding amounts of material at rates varying from one age period to another.

But fitting a curve to the individual values is the only way of extracting the maximum information about an individual's growth from the measurement data. This fact becomes increasingly inescapable when the effect of environmental circumstances on growth rate (e.g. illness on height growth) is investigated, or when two different measurements are being compared for the consistency of each as the child grows up. The individual's consistency can only be measured by deviations from his own growth curve. A change of rank order of two individuals in a measurement from one age to another may represent not inconsistency but consistently differing rates of change, one individual having a small velocity in the measurement and the other individual a larger one.

Very recently my colleague Dr M. Preece, in collaboration with Dr M. Baines of Reading University, has succeeded in formulating a curve which fits data on height and its components from soon after birth right up to maturity. The curve is at first the shape shown in Figure 2, but becomes s-shaped at adolescence. In its simpler form it has only four parameters (or constants) so that all the measurements of de Montbeillard's son, for example, can be subsumed in a set of four numbers. Previously it was necessary to use two curves, one up till and the other throughout adolescence.

Types of Growth Data

Such curves have to be fitted to data on single individuals. Curves of the yearly averages derived from different children each measured once only in general have a different shape. Thus the distinction between the two sorts of investigation is very important. The method of study using the same child at each age is called *longitudinal*; that using different children at each age is called *cross-sectional*. In a cross-sectional study each child is measured only once and all the children at age 10, for example, are different from those at age 9. A longitudinal study may extend over any number of years; there are short-term longitudinal studies extending from ages 3 to 5, for instance, and full birth-to-maturity longitudinal studies in which the children may be examined once, twice, or even more times every year from birth until 20 or over.

In practice it is always impossible to measure exactly the same group of children every year for a prolonged period; inevitably some children leave the study, and others, if that is desired, join it. A study in which this happens is called a *mixed longitudinal* study, and special statistical techniques are needed to get the maximum information out of its data. One particular type of mixed study is that in which a number of relatively short-term longitudinal groups are interlocked; for example, we may simultaneously study four groups, one followed from 0 to 6 years, the second from 5 to 11, the third 10 to 16, and the fourth 15 to 20. Thus the whole age-range is covered for estimates of mean yearly velocity in the research time of five years. However, problems arise at the 'joins' unless the sampling has been remarkably good.

Both cross-sectional and longitudinal studies have their uses, but they do not give the same information and cannot be dealt with in the same way. Cross-sectional surveys are obviously cheaper and more quickly done, and can include far larger numbers of children. They tell us a good deal about the curve of growth of height or weight for a given age (the 'distance' curve). It is essential to have cross-sectional surveys as part-basis for constructing standards for height and weight and other measurements in a given community, and periodic surveys are valuable in assessing the nutritional progress of a country or of particular socio-economic groups, or the health of the child population as a whole. But cross-sectional curveys have one great drawback; they can never reveal individual differences in rate or velocity of growth or in the timing of particular phases such as the adolescent growth spurt. It is these individual differences in growth velocity which chiefly throw light on the genetical control of growth and on the correlation of growth with psychological development, educational achievement and social behaviour. Longitudinal studies are laborious and time-consuming; they demand great perseverance on the part of those who make them and those who take part in them; and they demand very high technical standards, since, in the calculation of a growth increment from one occasion to the next, two errors of measurement occur. They demand also a sequential approach to problems, with all past data fully computerized and available for analysis in relation to a specific question at any time. The evidence of the past suggests that unless accompanied by cross-sectional surveys and animal experimentation, as they are, for example, at the Fels Research Institute in Yellow Springs, Ohio and at the Department of Growth and Development of the Institute of Child Health of London University, they can sink over the years into sterile deserts of number-collecting. But they are indispensable.

Cross-sectional data can be in some important respects misleading. Figure 3 illustrates the effect on 'average' figures produced by the individual differences in the age at which the adolescent spurt begins. Figure 3a shows a series of individual velocity curves from 10 to 18 years, each individual starting his spurt at a different age. The average of these curves, obtained simply by treating the values cross-sectionally and adding them up at ages 10, 11, 12, etc. and dividing by 5, is shown by the dashed line. This line in no way characterizes the 'average' velocity curve; on the contrary, it is a travesty of it. It smoothes out the adolescent spurt, spreading it along the time axis. It does not take account of the 'phase-differences' between the individual curves. Figure 3b shows the same individual curves, but arranged so that their peak velocities coincide; the average curve then characterizes the group in a proper manner. In passing from Figure 3a to 3b the time scale has been altered so that in 3b the curves are plotted not against chronological age but against a measure which arranges the children according to how far they have travelled along their course of development; in other words, they are arranged according to their true developmental or physiological growth-status. This is nearly always the appropriate method in analysing longitudinal data, especially at adolescence.

Averages computed from cross-sectional data, however, inevitably produce velocity curves of this flattened, distorted type;

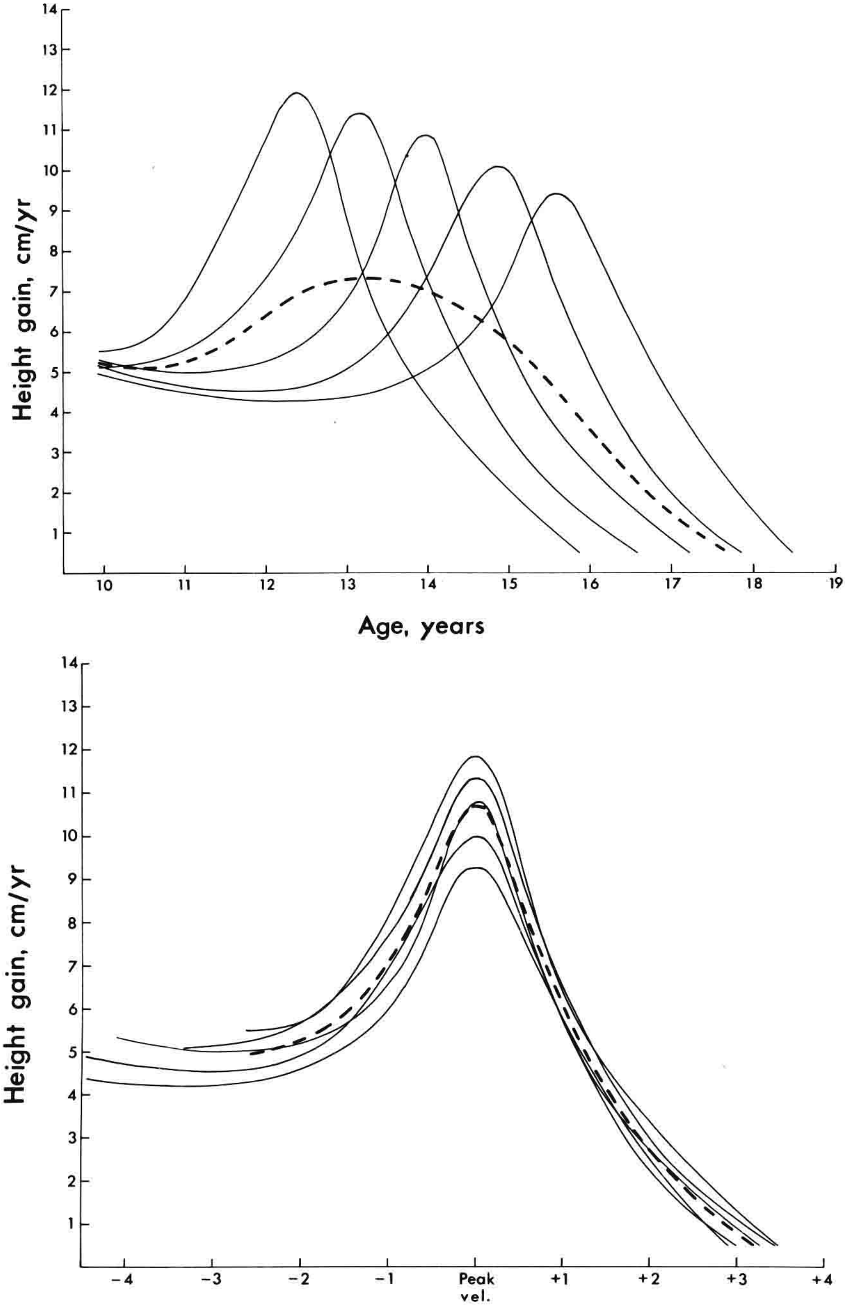

FIG. 3. The relation between individual and mean velocities during the adolescent spurt: (*above*) the individual height velocity curves of five boys of the Harpenden Growth Study (solid lines) with the mean curve (dashed) constructed by averaging their values at each age; (*below*) the same curves all plotted according to their peak height velocity
(From Tanner, Whitehouse and Takaishi, 1966)

and, equally, distance curves show the distortion by not rising sufficiently rapidly at adolescence.

Until recently all the published height and weight standards used in hospitals and schools incorporated this distortion. However, it is possible to construct a curve which represents the actual growth of a typical individual, by taking the shape of the curve from individual longitudinal data, and the absolute values for the beginning and end from large cross-sectional surveys. Figures 4 and 5 show height-attained and height velocity curves for the 'typical' boy and girl in Britain in 1965, determined in this way. By 'typical' is meant a boy or girl who has the mean birth length, grows always at the mean velocity, has the peak of the adolescent growth spurt at the mean age, and, finally, reaches the mean adult height at the mean age of cessation of growth. There is, of course, a certain danger in showing such a smooth, average curve, for measurements on a single individual are naturally less regular, however expert the measurer. Almost no individual exactly follows the curves of

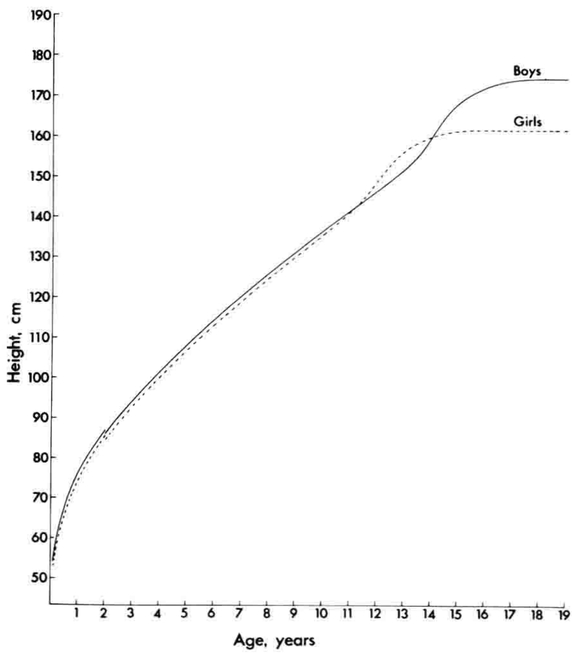

FIG. 4. Typical-individual height-attained curves for boys and girls (supine length to the age of 2; integrated curves of Fig. 5)
(From Tanner, Whitehouse and Takaishi, 1966)