This book is dedicated to our students, houseofficers and fellows for their constant vigilance, to our physician colleagues with whom we participate in a mutual responsibility to our patients and to our families without whose tolerance and patience this book would have been an even more arduous task.

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PREFACE

Bringing out the second edition of this textbook, predictably, has been a challenging experience. Quantum information leaps in Pediatric Endocrinology over the past seven years have necessitated the rewriting of nearly half the chapters and extensive revision of all the others. Many advances have been the result of careful clinical observation and this method of furthering the acquisition of knowledge continues to be the mainstay of learning in all clinical sciences. In the recent past, however, explosive advances in the basic sciences such as molecular biology, have provided us with new information on the pathogenesis of disease, new tools for diagnosis and new methods for the manufacture of therapeutic agents. As always, Endocrinology has been in the vanguard of the advance and it is no accident that two of the first agents for human use synthesized by molecular biological technology have been hormones, human insulin and human growth hormone.

The authors of the chapters of this book, whatever their expert knowledge of these new fields of endeavor, have never lost sight of the goals and title of this book, that this is a book by clinicians for clinicians. Our objective has been to provide guidance for the physician caring for pediatric patients with endocrine problems. We have not shied away from covering the necessary background for the clinical information contained in its pages but we have done our best to avoid lengthy forays into the areas of biochemistry, molecular biology and neuroanatomy. For those interested, an extensive bibliography lists sources where this information may be obtained in greater detail.

Comprehensive reorganization of this second edition has resulted in the reordering of the list of contributors to the first edition with the inevitable substitution for respected authorities, but with the assembly of what the editor believes is the best roster of experts available to him. We express our sorrow at the passing of one of our most illustrious contributors to the first edition, Alfred Bongiovanni, whose death is mourned by his many friends and colleagues throughout the world. His pioneering contributions to the field of Pediatric Endocrinology will assure a respected place for him in the history of our specialty and of medical science in general.

I wish to express my thanks to the contributors to this book who met their deadlines and enabled us to expedite its publication. Also I wish to thank my colleague Dr. S. Douglas Frasier who kindly edited my contribution. Finally, I wish to thank the many readers of the first edition who generously offered comments and suggestions that were invaluable in the planning and writing of the second edition.

Solomon A. Kaplan

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1

GROWTH AND GROWTH HORMONE: Disorders of the Anterior Pituitary

Solomon A. Kaplan

NORMAL GROWTH[1,2]

The term *growth* is used to describe change in size with maturation. Normal growth can occur only if the individual is healthy. Thus, measurement of height and weight is an essential part of the physical examination to determine if the individual's health is normal. Acute illnesses do not impair growth significantly, but long-standing illness of the bowel, kidney, heart, lung, and so on may lead to marked change in growth rate. Physicians who take care of children should have measuring devices available that permit an accurate determination of *length*. Children who can stand erect steadily should have their height measured by a device that is fixed to a wall or some other sturdy support. The standing height is best measured by having the subject stand with heels, buttocks, thoracic spine, and head touching the device. It is advisable to have the subject stand as tall or erect as possible to counter the slouching that tends to become more marked as the day progresses. A sliding device that projects from the measuring device and is made to rest firmly on the subject's head is useful in providing reproducible measurements.

"Stadiometers" have also been used to measure height. These somewhat more expensive instruments have self-balancing devices that do not require the head-measuring block to be held in the hand. In that case the measurer is free to use the hands to raise the subject to full height by upward pressure on the mandibular rami. For infants a useful device is a boxlike structure that accommodates the head on one side and has a movable slab to press against the soles of the feet on the other. Length measurements of infants are particularly difficult to make, and erroneous results are obtained unless great care is exercised. *Sitting height* is a most important measurement for any child with a growth disturbance and is measured by seating the subject on a box with the back resting against the measuring device. In general, measurements of sitting height are more accurate in determining the relative lengths of the legs and trunk than measurements of the distances between the pubic tubercles and the top of the head and bottoms of the feet.

Standards of growth have been compiled by the National Center for Health Statistics of the United States Government. These standards are based on accurate measurements made on large, nationally representative samples of children. Seven centiles (5, 10, 25, 50, 75, 90, and 95) have been calculated for both height and weight. The growth measurements are listed in Tables 1–1, 1–2, 1–3, 1–4, and 1–5. Growth charts based on these data are available and are most useful in diagnosis and treatment of growth problems (Figs. 1–1, 1–2, 1–3, and 1–4). The charts are applicable to virtually all racial groups in the United States provided the growth patterns of the parents are taken into account.

To determine if a child is abnormally short when his or her parents are short one can use the following maneuver. Obtain the derived midparental height by averaging the parents' heights after first adding 13 cm to the mother's height if the subject is a boy or subtracting 13 cm from the father's height if the subject is a girl. Determine the growth

TABLE 1–1. SMOOTHED CENTILES OF RECUMBENT LENGTH IN CENTIMETERS, FOR MALES AND FEMALES, BIRTH TO 36 MONTHS*

Sex and Age	Centile						
	5th	10th	25th	50th	75th	90th	95th
Male							
Birth	46.4†	47.5	49.0	50.5	51.8	53.5	54.4
1 month	50.4	51.3	53.0	54.6	56.2	57.7	58.6
3 months	56.7	57.7	59.4	61.1	63.0	64.5	65.4
6 months	63.4	64.4	66.1	67.8	69.7	71.3	72.3
9 months	68.0	69.1	70.6	72.3	74.0	75.9	77.1
12 months	71.7	72.8	74.3	76.1	77.7	79.8	81.2
18 months	77.5	78.7	80.5	82.4	84.3	86.6	88.1
24 months	82.3	83.5	85.6	87.6	89.9	92.2	93.8
30 months	87.0	88.2	90.1	92.3	94.6	97.0	98.7
36 months	91.2	92.4	94.2	96.5	98.9	101.4	103.1
Female							
Birth	45.4	46.5	48.2	49.9	51.0	52.0	52.9
1 month	49.2	50.2	51.9	53.5	54.9	56.1	56.9
3 months	55.4	56.2	57.8	59.5	61.2	62.7	63.4
6 months	61.8	62.6	64.2	65.9	67.8	69.4	70.2
9 months	66.1	67.0	68.7	70.4	72.4	74.0	75.0
12 months	68.8	70.8	72.4	74.3	76.3	78.0	79.1
18 months	76.0	77.2	78.8	80.9	83.0	85.0	86.1
24 months	81.3	82.5	84.2	86.5	88.7	90.8	92.0
30 months	86.0	87.0	88.9	91.3	93.7	95.6	96.9
36 months	90.0	91.0	93.1	95.6	98.1	100.0	101.5

* Statistics from National Center for Health Statistics. See reference 1 for method of smoothing by cubic-spline approximation.
† Recumbent length given in centimeters.

TABLE 1–2. SMOOTHED CENTILES OF WEIGHT IN KILOGRAMS, FOR MALES AND FEMALES, BIRTH TO 36 MONTHS*

Sex and Age	Centile						
	5th	10th	25th	50th	75th	90th	95th
Male							
Birth	2.54†	2.78	3.00	3.27	3.64	3.82	4.15
1 month	3.16	3.43	3.82	4.29	4.75	5.14	5.38
3 months	4.43	4.78	5.32	5.98	6.56	7.14	7.37
6 months	6.20	6.61	7.20	7.85	8.49	9.10	9.46
9 months	7.52	7.95	8.56	9.18	9.88	10.49	10.93
12 months	8.43	9.84	9.49	10.15	10.91	11.54	11.99
18 months	9.59	9.92	10.67	11.47	12.31	13.05	13.44
24 months	10.54	10.85	11.65	12.59	13.44	14.29	14.70
30 months	11.44	11.80	12.63	13.67	14.51	15.47	15.97
36 months	12.26	12.69	13.58	14.69	15.59	16.66	17.28
Male							
Birth	2.36	2.58	2.93	3.23	3.52	3.64	3.81
1 month	2.97	3.22	3.59	3.98	4.36	4.65	4.92
3 months	4.18	4.47	4.88	5.40	5.90	6.39	6.74
6 months	5.79	6.12	6.60	7.21	7.83	8.38	8.73
9 months	7.00	7.34	7.89	8.56	9.24	9.83	10.17
12 months	7.84	8.19	8.81	9.53	10.23	10.87	11.24
18 months	8.92	9.30	10.04	10.82	11.55	12.30	12.76
24 months	9.87	10.26	11.10	11.90	12.74	13.57	14.08
30 months	10.78	11.21	12.11	12.93	13.93	14.81	15.35
36 months	11.60	12.07	12.99	13.93	15.03	15.97	16.54

* Statistics from National Center for Health Statistics. (see legend for Table 1–1).
† Weight given in kilograms.

TABLE 1–3. SMOOTHED CENTILES OF STATURE IN CENTIMETERS, FOR MALES AND FEMALES, 2 TO 18 YEARS*

Sex and Age	Centile						
	5th	10th	25th	50th	75th	90th	95th
Male							
2.0 years	82.5†	83.5	85.3	86.8	89.2	92.0	94.4
3.0 years	89.0	90.3	92.6	94.9	97.5	100.1	102.0
4.0 years	95.8	97.3	100.0	102.9	105.7	108.2	109.9
5.0 years	102.0	103.7	106.5	109.9	112.8	115.4	117.0
6.0 years	107.7	109.6	112.5	116.1	119.2	121.9	123.5
7.0 years	113.0	115.0	118.0	121.7	125.0	127.9	129.7
8.0 years	118.1	120.2	123.2	127.0	130.5	133.6	135.7
9.0 years	122.9	125.2	128.2	132.2	136.0	139.4	141.8
10.0 years	127.7	130.1	133.4	137.5	141.6	145.5	148.1
11.0 years	132.6	135.1	138.7	143.3	147.8	152.1	154.9
12.0 years	137.6	140.3	144.4	149.7	154.6	159.4	162.3
13.0 years	142.9	145.8	150.5	156.5	161.8	167.0	169.8
14.0 years	148.8	151.8	156.9	163.1	168.5	173.8	176.7
15.0 years	155.2	158.2	163.3	169.0	174.1	178.9	181.9
16.0 years	161.1	163.9	168.7	173.5	178.1	182.4	185.4
17.0 years	164.9	167.7	171.9	176.2	180.5	184.4	187.3
18.0 years	165.7	168.7	172.3	176.8	181.2	185.3	187.6
Female							
2.0 years	81.6	82.1	84.0	86.8	89.3	92.0	93.6
3.0 years	88.3	89.3	91.4	94.1	96.6	99.0	100.6
4.0 years	95.0	96.4	98.8	101.6	104.3	106.6	108.3
5.0 years	101.1	102.7	105.4	108.4	111.4	113.8	115.6
6.0 years	106.6	108.4	111.3	114.6	118.1	120.8	122.7
7.0 years	111.8	113.6	116.8	120.6	124.4	127.6	129.5
8.0 years	116.9	118.7	122.2	126.4	130.6	134.2	136.2
9.0 years	122.1	123.9	127.7	132.2	136.7	140.7	142.9
10.0 years	127.5	129.5	133.6	138.3	142.9	147.2	149.5
11.0 years	133.5	135.6	140.0	144.8	149.3	153.7	156.2
12.0 years	139.8	142.3	147.0	151.5	155.8	160.0	162.7
13.0 years	145.2	148.0	152.8	157.1	161.3	165.3	168.1
14.0 years	148.7	151.5	155.9	160.4	164.6	168.7	171.3
15.0 years	150.5	153.2	157.2	161.8	166.3	170.5	172.8
16.0 years	151.6	154.1	157.8	162.4	166.9	171.1	173.3
17.0 years	152.7	155.1	158.7	163.1	167.3	171.2	173.5
18.0 years	153.6	156.0	159.6	163.7	167.6	171.0	173.6

* Statistics from National Center for Health Statistics (see legend for Table 1–1).
† Stature given in centimeters.

centile on which the midparental height falls. Extrapolation of the child's anticipated growth along his or her channel, taking the skeletal age into account, should yield an adult height within plus or minus 5 cm of the derived mean adult height. If the growth extrapolation is different from the midparental height by 5 cm or more, then the growth of the child should not be ascribed simply to parental short stature.

Growth increments are most important criteria on which to base a diagnosis of the cause of short stature. Irrespective of where the child's height or weight is found to plot on the growth curve, if the increment in growth over the recent 6 or 12 months is normal, it is most unlikely that an active disorder impairing growth exists in the individual. Children recovering from an illness or undergoing treatment for one or children with idiopathic growth delay, after an initial period of growth delay, will show normal or greater than normal growth increments. For example, if the height measurement of a child plots below the 5th centile on the growth chart, and if the height increment over a period of 6 months or 1 year is normal, it is improbable that the child is suffering from an active disorder leading to growth failure. Growth increments normally vary considerably throughout the life of the child. The normal growth increment in the first 6 months of life is 16 to 17 cm and in the second 6 months about 8 cm. In the sec-

TABLE 1–4. SMOOTHED CENTILES OF WEIGHT IN KILOGRAMS, FOR MALES AND FEMALES, 2 TO 18 YEARS*

Sex and Age	Centile						
	5th	10th	25th	50th	75th	90th	95th
Male							
2.0 years	10.49†	10.96	11.55	12.34	13.36	14.38	15.50
3.0 years	12.05	12.58	13.52	14.62	15.78	16.95	17.77
4.0 years	13.64	14.24	15.39	16.69	17.99	19.32	20.27
5.0 years	15.27	15.96	17.22	18.67	20.14	21.70	23.09
6.0 years	16.93	17.72	19.07	20.69	22.40	24.31	26.34
7.0 years	18.64	19.53	21.00	22.85	24.94	27.36	30.12
8.0 years	20.40	21.39	23.09	25.30	27.91	31.06	34.51
9.0 years	22.25	23.33	25.40	28.13	31.46	35.57	39.58
10.0 years	24.33	25.52	28.07	31.44	35.61	40.80	45.27
11.0 years	26.80	28.17	31.25	35.30	40.38	46.57	51.47
12.0 years	29.85	31.46	35.09	39.78	45.77	52.73	58.09
13.0 years	33.64	35.60	39.74	44.95	51.79	59.12	65.02
14.0 years	38.22	40.64	45.21	50.77	58.31	65.57	72.13
15.0 years	43.11	46.06	50.92	56.71	64.72	71.97	79.12
16.0 years	47.74	51.16	56.16	62.10	70.26	77.97	85.62
17.0 years	51.50	55.28	60.22	66.31	74.17	83.58	91.31
18.0 years	53.97	57.89	62.61	68.88	76.04	88.41	95.76
Female							
2.0 years	9.95	10.32	10.96	11.80	12.73	13.58	14.15
3.0 years	11.61	12.26	13.11	14.10	15.50	16.54	17.22
4.0 years	13.11	13.84	14.80	15.96	17.56	18.93	19.91
5.0 years	14.55	15.26	16.29	17.66	19.39	21.23	22.62
6.0 years	16.05	16.72	17.86	19.52	21.44	23.89	25.75
7.0 years	17.71	18.39	19.78	21.84	24.16	27.39	29.68
8.0 years	19.62	20.45	22.26	24.84	27.88	32.04	34.71
9.0 years	21.82	22.92	25.27	28.46	32.44	37.60	40.64
10.0 years	24.36	25.76	28.71	32.55	37.53	43.70	47.17
11.0 years	27.24	28.97	32.49	36.95	42.84	49.96	54.00
12.0 years	30.52	32.53	36.52	41.53	48.07	55.99	60.81
13.0 years	34.14	36.35	40.65	46.10	52.91	61.45	67.30
14.0 years	37.76	40.11	44.54	50.28	57.09	66.04	73.08
15.0 years	40.99	43.38	47.82	53.68	60.52	69.54	77.78
16.0 years	43.41	45.78	50.09	55.89	62.29	71.68	80.99
17.0 years	44.74	47.04	51.14	56.69	62.91	72.38	82.46
18.0 years	45.26	47.47	51.39	56.62	62.78	72.25	82.47

* Statistics from National Center for Health Statistics (see legend for Table 1–1).
† Weight given in kilograms.

ond year growth normally exceeds 10 cm, in the third year it exceeds 8 cm, and in the fourth year 7 cm. Between the fourth and 10th years the growth rate is 5 to 6 cm per year. In general, if the growth increment of the subject is within the normal range, it is unlikely that active or progressive disease is present. Assessment of the normal growth velocity for a particular age span can be made by measuring the growth increment along the 50th centile of the growth chart for that age span. Charts depicting normal growth velocities for height have been developed by Tanner and Davies,[3] and are available commercially.

Growth of the Osseous System[4,5]

The major factor contributing to growth is the lengthening of the skeleton. Longitudinal growth of the bones occurs by endochondral ossification, in which growth of the bone occurs by transformation of cartilage into osseous tissue. This process of endochondral ossification occurs largely in the tubular bones of the extremities but is also characteristic of the vertebral bodies. Increase in width of bones occurs from development of skeletal tissue directly from fibrous membrane. This is the mechanism by which thickening of the bones of the calvarium, the flat parts of the pelvis and sca-

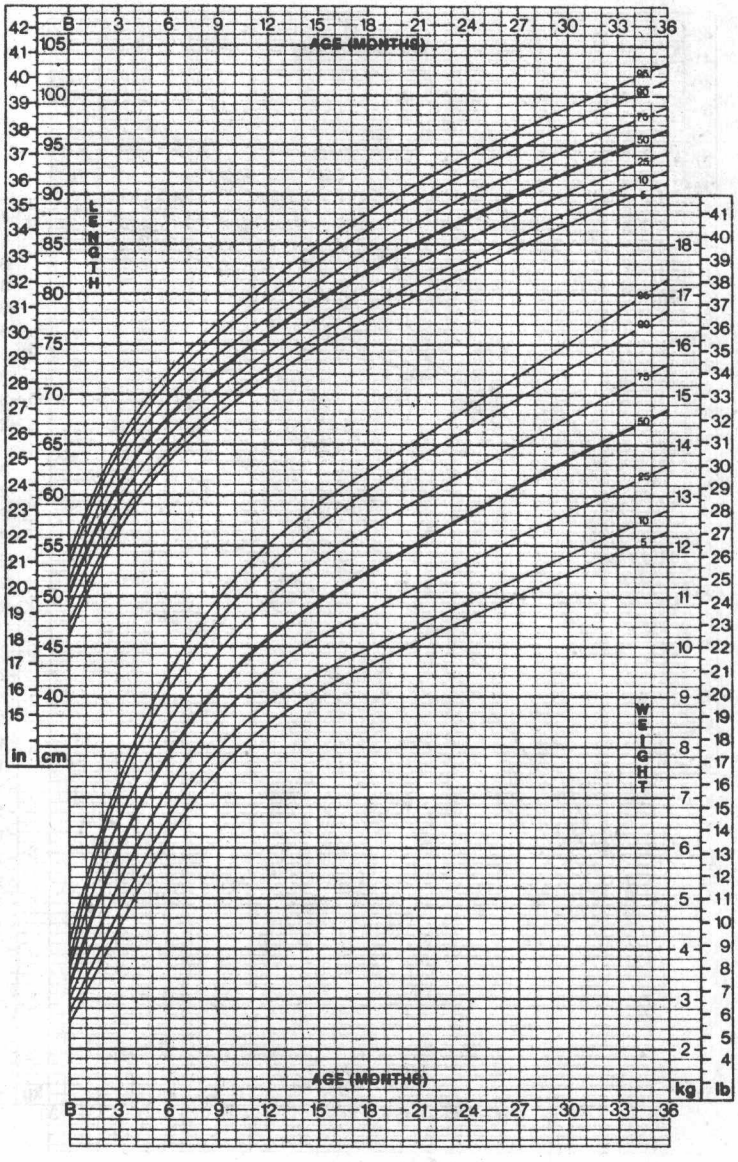

FIGURE 1–1. NCHS centiles for length and weight for age, boys, birth to 36 months. (From Moore WM: Children are different. *In* Johnson TR, Moore WM (eds): Physical Growth. Columbus, OH, Ross Laboratories, 1978, p 16.)

pulae, and the body of the mandible occurs. The diaphysis of tubular bones of the extremities also thickens by the laying down of bone directly from the fibrous periosteum. In general, length of bones is increased by the process of growth in cartilage, or endochondral ossification, while increase in the girth of bones occurs through membranous ossification.

The first signs of endochondral ossification begin in the fetus during the seventh week, and growth begins to spread from the center of the bone, which is referred to as the primary center. Subsequently, secondary centers of ossification develop in many bones, usually at a much later date and at other sites, mostly at the extremities of the bone. Initially cartilage undergoes ossification in fetal life, but this process is short lived, as osteoclasts invade the cartilage with proliferation of the blood vessels. Accompanying the proliferation of blood vessels are the bone-forming cells, osteoblasts, which form layers of bone on those remnants of the calcified cartilage that have not been destroyed by the osteoclasts. The development of cavities in spongy bone is the result of osteoclastic activity. In a bone such as the femur, none of the bony tissue present in the adult was present at birth because the size of the marrow cavity in the adult is greater than the size of the femur at birth.

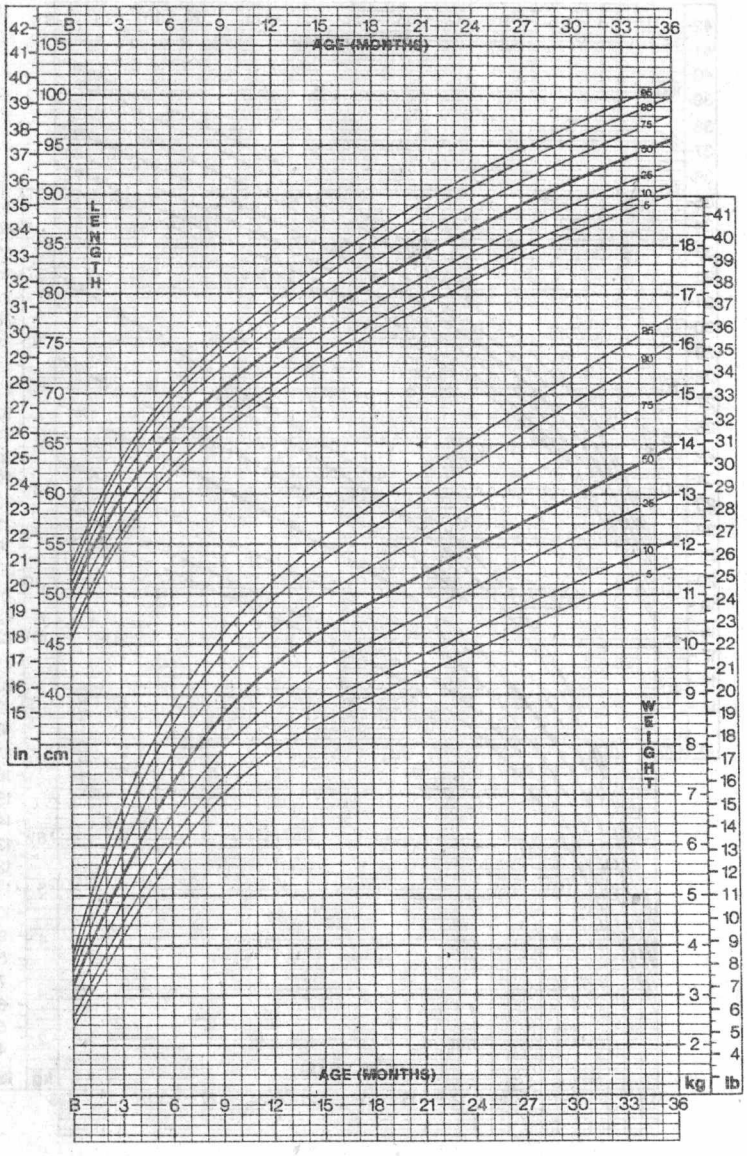

FIGURE 1–2. NCHS centiles for length and weight for age, girls, birth to 36 months. (From Moore WM: Children are different. *In* Johnson TR, Moore WM (eds): Physical Growth. Columbus, OH, Ross Laboratories, 1978, p 18.)

This example illustrates the marked turnover of structures that occurs from the inception of development of a bone until its growth ceases. Even after growth ceases, turnover of calcium and other chemical components of the bone continues actively.

While many short or flat bones ossify entirely from the primary center, all the long bones and some of the flat bones develop secondary centers that appear in the cartilage of the extremities of the bone. With few exceptions these secondary centers appear after birth. Ossification in these centers proceeds in a manner identical to that in the primary centers, with ossification of cartilage and invasion of osteoclasts and osteoblasts. The part of the bone ossified from the primary center is the diaphysis, while the part developed from the secondary center is referred to as the epiphysis. As the secondary center is progressively ossified, the cartilage is replaced by bone until only a thin plate of cartilage, the epiphyseal plate, separates the diaphyseal bone from the epiphysis. The part of the diaphysis that abuts on the epiphysis is referred to as the metaphysis and represents the growing end of the bone. As long as the epiphyseal cartilage plate persists, both the diaphysis and epiphysis continue to grow, the growth being much greater in the diaphysis. Eventually the osteoblasts cease to multiply, and the

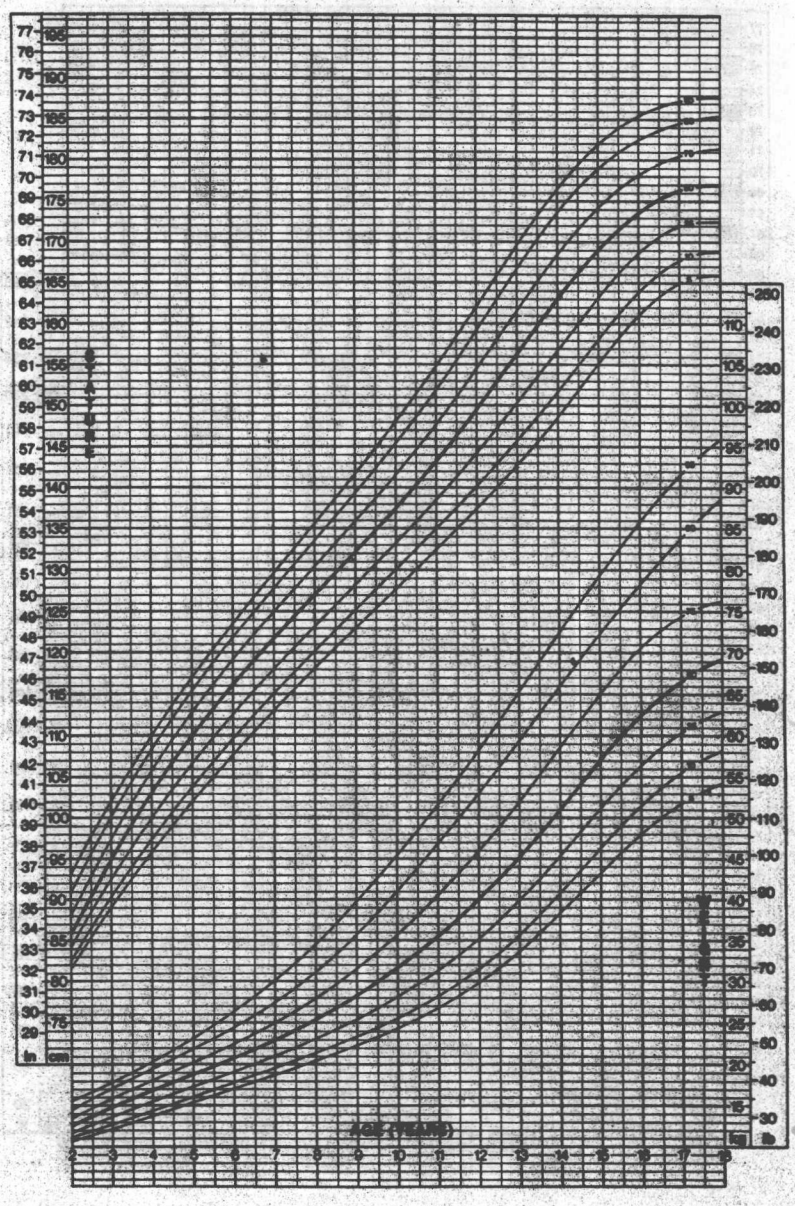

FIGURE 1–3. NCHS centiles for stature and weight for age, boys, 2 to 18 years. (From Moore WM: Children are different. *In* Johnson TR, Moore WM (eds): Physical Growth. Columbus, OH, Ross Laboratories, 1978, p 20.)

epiphyseal plate is ossified. The osseous structures of the diaphysis and epiphysis are fused and growth ceases. If the bone forms part of a joint, however, articular cartilage persists. This articular cartilage does not participate in further growth of the bone.

Skeletal Age

The length of an individual is determined by the length of the skeleton, growth of which is determined largely by lengthening of the diaphysis. In bones with normal structure (e.g., those that are not affected by skeletal dysplasia) the growth potential of the diaphysis depends on the progression of ossification within the epiphysis. It is possible to assess the growth potential of the bone by the degree of ossification of the epiphysis. It was first recognized that epiphyseal ossification was severely delayed in hypothyroidism, but it has been established that many other factors influence the progression of epiphyseal ossification. Measurement of epiphyseal center development or skeletal age has become a valuable tool in the classification of growth retardation and in the prediction of ultimate height.

The first standards for skeletal age were established by Todd in 1937 and subse-

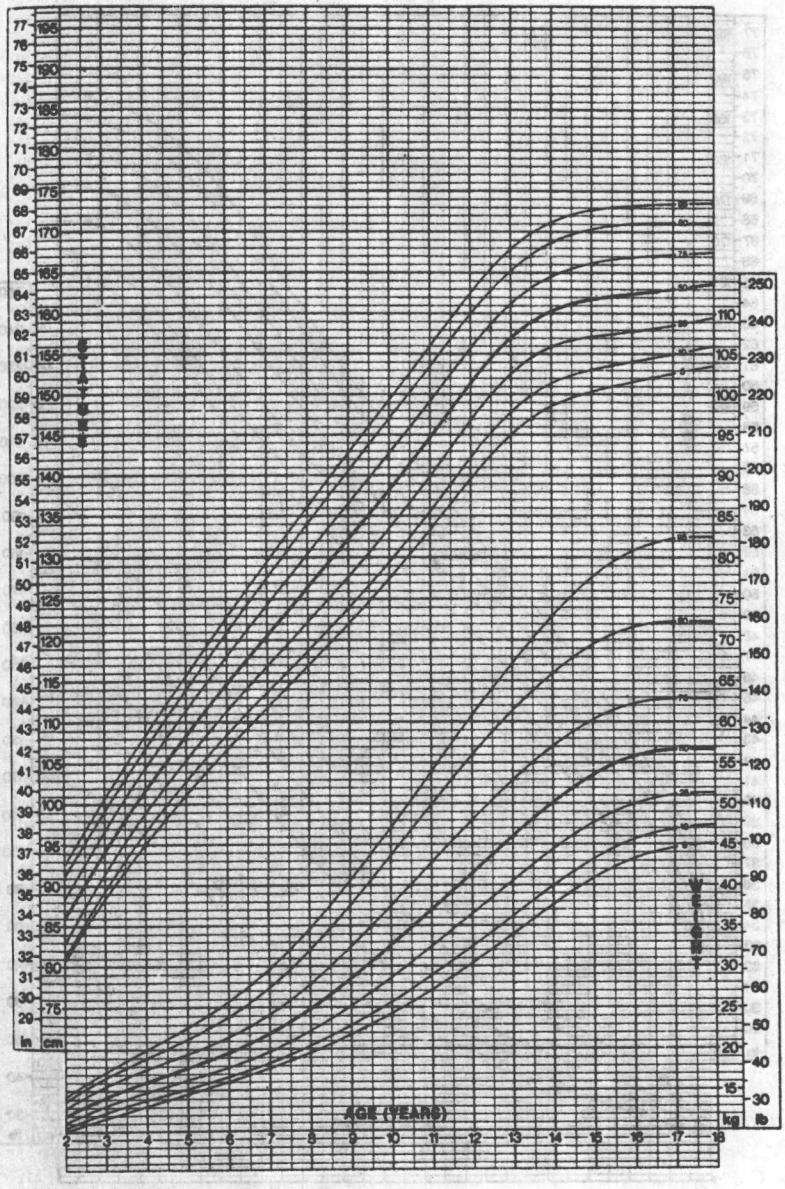

FIGURE 1–4. NCHS centiles for stature and weight for age, girls, 2 to 18 years. (From Moore WM: Children are different. *In* Johnson TR, Moore WM (eds): Physical Growth. Columbus, OH, Ross Laboratories, 1978, p 21.)

quently further developed by Greulich and Pyle.[5] Radiographs of the bones of an individual are compared with the normal standards, and the individual is assigned a skeletal age. Thus a convenient means is available for expressing the potential for growth of the individual.

Several methods for the assessment of skeletal age have been developed, and there is no unanimous agreement on which method is best. Examination of radiographs of all bones of the body of a growing child would be tedious and expensive, and the radiation exposure would be undesirable. Considerable effort has been made, therefore, to determine if a portion of the skeleton could be used as an index of development of the rest of the skeleton. Although the hand and wrist do not contribute to the height of the individual, radiographs of this part of the body have proven valuable in assessment of skeletal age. Discrepancies between the two sides are generally insignificant, and standards have been developed that use only the left hand and wrist. Using the radiographs of 100 normal children, Greulich and Pyle compiled the *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, the second edition of which was published in 1959 and is cur-

TABLE 1–5. MEAN SITTING HEIGHT TO LOWER SEGMENT RATIOS*

Age (Years)	Boys	Girls
0.5–1.4	1.81	1.86
1.5–2.4	1.61	1.80
2.5–3.4	1.47	1.44
3.5–4.4	1.36	1.36
4.5–5.4	1.30	1.29
5.5–6.4	1.25	1.24
6.5–7.4	1.20	1.21
7.5–8.4	1.16	1.16
8.5–9.4	1.13	1.14
9.5–10.4	1.12	1.11
10.5–11.4	1.10	1.08
11.5–12.4	1.07	1.07
12.5–13.4	1.06	1.07
13.5–14.4	1.04	1.09
14.5–15.4	1.05	1.10
15.5–16.4	1.07	1.12
16.5–17.4	1.08	1.12
17.5–18.4	1.09	1.12

* Calculated from data taken from Bayer LM, Bayley N: Growth Diagnosis. Chicago, University of Chicago Press, 1959.

rently used extensively.[5] The standards of males differ from those of females, especially in the adolescent years, but significant differences may be found at other ages. The films chosen for the *Atlas* were radiographs of children no more than 2 per cent older or younger than the age represented, and those chosen for inclusion in the *Atlas* represented the best approximation to the anatomic mode. In many instances films covering several examinations from the same individual were used. For the first 18 months of age, the standards are 3 months apart but, subsequently, longer intervals of time separate the standards.

In interpreting the films, account is taken of distal parts of the radius and ulna, the carpals, the metacarpals, and all the phalanges. A careful and detailed comparison of each bone of the subject with the standard is necessary, and it is preferable to proceed in a predetermined order to examine each bone. The *Atlas* provides descriptions of the features of the bones that should be assessed as well as line drawings of these features.

It is well to recognize that sources of error exist in the interpretation of skeletal age films and that such interpretation must be made with great caution. A problem frequently encountered is one of discrepancy between different centers and, often, the development of the carpal bones does not correlate well with the development of the distal centers. It has long been known that different centers have different degrees of predictive value in terms of potential growth. The relative value of different centers has been assessed by Garn and associates by longitudinal evaluation of radiographic information on the skeletal development of a large number of boys and girls and its correlation with the age of appearance of other centers.[6] The predictive ranking varies between boys and girls. In boys, the predictive ranking for epiphyseal centers in the hand was highest for the distal segment of the fifth, fourth, and third fingers, followed by the epiphysis of the third metacarpal. The lowest predictive ranking was found for the carpal capitate, lunate, and hamate centers. For girls, the epiphyses of the third, fifth, and fourth metacarpals gave the highest orders of ranking in the hand and wrist; the lowest rankings were given by the carpal capitate, lunate, and hamate. None of the carpal bones of the hand was listed in the top 20 for either sex.

More recently, Tanner and Whitehouse have attempted to refine the method of assessment of skeletal age by establishing a series of standard appearances or stages through which each bone passes.[7] Each bone of the radiograph of the subject's hand is matched with the standard and is assigned a numerical score. The scores are summed to give a skeletal maturity score for the whole hand and wrist. A centile status in skeletal maturity is then assigned to the subject just as it is for height and weight. Originally the Tanner-Whitehouse system did not discriminate between the sexes, but in the revised system, the Tanner-Whitehouse 2 system, girls and boys are assigned somewhat different scores for each stage of bone development. At any age the total score is higher for girls than for boys. Separate standards are given for bone age based only on the radius, ulna, metacarpals, and phalanges (RUS) or only on the carpal bones.

Delay in osseous maturation is paralleled by delay in dental maturation to a large degree. Tooth formation and status of eruption as seen in radiographs may be used to develop an assessment of *dental age*.[6] Perhaps because it involves additional radiation exposure, this assessment is not usually a part of the clinical investigation of children with short stature. However, clinical examination of the teeth to determine their eruption pattern and questions regarding the time of appearance of both deciduous and permanent

teeth are most useful in predicting whether skeletal age may be delayed.

Determination of skeletal age is perhaps the most important laboratory test used in determining the etiology of growth disorders and the prognosis for children with them. It is important to realize, however, that errors in interpretation frequently occur. These can be minimized if the films are interpreted by an individual with experience in reading them and if comparisons are made with films taken previously. At any age the standard deviation for interpretation is about 10 per cent of the chronologic age. By and large, when there is a discrepancy between the carpal bones and the distal centers, it is better to assign greater weight to the distal centers because they tend to correlate better with growth potential.

Although the standards of the *Atlas* are based largely on Caucasian children, they may be used for other racial groups living in the United States. The osseous maturation of American-born Japanese children was found to be much closer to that of Caucasian-American children than to that of Japanese living in Japan in the first few years after World War II. Genetic factors also contribute to the pattern of osseous maturation. Significant parent-child similarities in hand-wrist ossification have been found to occur, and (as will be discussed later in greater detail) ossification patterns found in individuals with inherited skeletal dysplasias may be detectable in their parents and siblings.

Knowledge of skeletal age is of great importance in the diagnosis and treatment of infants and children with growth disorders for two reasons. First, growth retardation is classified into two broad categories depending on whether (1) there is an intrinsic disease of the bone that has led to shortening of the diaphysis without significant delay of epiphyseal maturation or (2) there are factors outside the skeletal system that impair growth and epiphyseal maturation, such as hypothyroidism or malnutrition. Thus, evaluation of the skeletal age greatly assists in the diagnosis of the cause or category of growth retardation. Second, the growth potential of the individual can be estimated from the individual's height at the time of examination and the skeletal age. It is necessary to realize, however, that any such prediction is only a rough estimate and attempts at accurate prediction are unwise. Several reasons for this exist. It has been pointed out that accurate skeletal age interpretation may be quite difficult and that significant errors are made even by experienced observers. In addition, progression of skeletal age does not necessarily parallel height increments, particularly in children with skeletal dysplasia. A similar discrepancy often occurs in children treated over several years for severe hypothyroidism. Discordance between skeletal development and growth is particularly likely to occur in children with sexual precocity, in whom estrogens and androgens produced in excess generally accelerate skeletal age to a greater degree than height age.

Tables for prediction of ultimate height based on the individual's height, skeletal age, sex, age, and growth rate have been published.[5,8] Using skeletal age for prediction of ultimate height it is also possible to make a rough calculation as follows. Measure the individual's height, plot it on a standard growth curve, and extrapolate the value horizontally to the age on the chart that is equal to the bone age. If the point of extrapolation falls between the 5th and 95th centiles, then a guarded prediction of normal adult stature can be given. The closer the extrapolated value is to the 50th centile, the more good reason there is for optimism.

Growth deficiency may be classified into two broad categories:

Primary growth deficiency: In this category there is an intrinsic defect in the skeletal system as a result of either a genetic defect of or prenatal damage to the skeletal system. In this form of growth disorder the potential normal bone growth (and, therefore, body growth) is impaired. Skeletal age is not delayed or is delayed much less than is height age.

Secondary growth deficiency: Growth is retarded because factors, generally outside the skeletal system, delay osseous maturation. These factors may be endocrine, nutritional, metabolic, or unknown, as in the syndrome of idiopathic (constitutional) growth delay. In this form of growth retardation the skeletal age and the height age may be delayed to nearly the same degree. (Height age of an individual is defined as the age at which the individual's height is at the 50th centile.) In secondary growth deficiency, the potential often exists for reaching normal adult height.

A distinction between these two categories of growth impairment is necessary because their causes, prognoses, and diagnostic approaches are different. Difficulties with this classification may arise in some instances in which the skeletal age is delayed to a lesser