MEDICAL GRAND ROUNDS

September 21, 1967

ENDOCRINE PROBLEMS OF ADOLESCENCE - THE SHORT AND THE TALL

Adolescence: The transitional period between puberty and adulthood.

I. The Mechanisms, Patterns and Variations of Normal Adolescence

A. The initiation of adolescence

1. The brain controls the initiation

a. A pituitary transplanted from a newborn rat into an adult begins to secrete gonadotropins long before the donor rat would have reached puberty (Harris and Jacobsohn. Proc. Roy. Soc. B. 139:263, 1952).

b. An interesting hypothesis has been proposed by Donovan and Van der Werff ten Bosch (Physiology of Puberty, Williams & Wilkins, Baltimore, 1965). "Before puberty, the hypothalamus is very highly sensitive to estrogens and the change occurring at puberty is a decrease in this sensitivity of hypothalamic cells." The normally low estrogen level of the prepubertal animal had been adequate to inhibit the hypothalamus. Now, the hypothalamus is no longer inhibited and releases stimuli to the pituitary to secrete gonadotropins. "Gonadotropins rise until they cause a rise in estrogen sufficient, on the one hand, to inhibit the mature hypothalamus, and, on the other, to cause growth of the female secondary sex characters."

c. Though evidence for such an hypothesis in man is lacking, there are numerous instances of precocious puberty of cerebral origin, showing that the brain initiates the events of adolescence in man no less than in the rat.

2. The timing of normal puberty - may start from age 9 to 17

a. "Average" - from Wilkins Text, p. 201.

Age	Boys	Girls
9-10		Growth of bony pelvis, budding of nipples
10-11	Growth of testes & penis	Budding of breasts, pubic hair
11-12	Prostatic growth	Growth of genitalia, changes in vaginal epithelium
12-13	Pubic hair	Growth of breasts, darkening of nipples
13-14	Rapid growth of testes	Menarche; axillary hair
14-15	Voice change, axillary hair	Earliest normal pregnancy
15-16	Spermatogenesis complete	Acne, deepening of voice
16-17	Acne, facial & body hair	Cessation of skeletal growth
19-21	Cessation of skeletal growth	

b. Wide range of time on onset - Percentage of normal boys starting puberty (from Schonfeld, A.M.A.J. Dis. Child. 65:535, 1943).

1) Age 10 = 4%
2) Age 11 = 24%
3) Age 12 = 56%
4) Age 13 = 85%
5) Age 14 = 94%

c. Table I lists average (50 percentile) measurements

TABLE I

AVERAGE NORMAL MEASUREMENTS (In Inches and Pounds)

	BOYS					GIRLS				
Age Yrs.	Height In.	Height Annual Incr.	Weight (lb)	Ratio U/L (from symphysis)	Span minus Height	Height In.	Height Annual Incr.	Weight (lb)	Ratio U/L (from symphysis)	Span minus Height
Birth	20.0		7.5	1.70	-1.0	20.0		7.0	1.70	-1.0
3	38.0	3.6	33.5	1.33	-1.1	37.6	3.7	32.5	1.30	-1.6
6	46.3	2.7	48.2	1.12	-1.0	46.3	2.8	48.3	1.10	-1.3
9	53.3	2.2	68.4	1.02	0	53.3	2.2	69.6	1.01	0.5
10	55.5	2.2	76.8	0.99	0	55.5	2.2	78.1	1.00	0.4
11	57.4	1.9	85.6	0.98	0	58.1	2.6	88.4	0.99	0
12	59.6	2.2	95.2	0.98	+0.8	60.7	2.6	100.4	0.99	0
13	62.0	2.4	105.7	0.97	+1.3	62.8	2.1	110.5	1.00	0
14	64.9	2.9	119.1	0.97	+1.3	64.1	1.3	120.1	1.01	0
15	67.4	2.5	132.3	0.98	+1.7	64.9	0.8	126.6	1.01	+0.5
16	69.0	1.6	141.9	0.99	+1.8	65.2	0.3	130.5	1.01	+0.5
17	69.5	0.5	147.6	0.99	+2.1	65.2	0	133.5	1.01	+0.5

Source: Wilkins, L. Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, 3rd Edition, p. 32.

B. The endocrinology of adolescence

1. Anterior pituitary

a. Size

1) Weight of gland: At birth = 0.1 Gm, Age 10 = 0.25 Gm, Age 16 = 0.35 Gm in males, 0.5 Gm in females.
2) Area of sella turcica - as shown by Riach (Brit. J. Radiology 39:241, April, 1966), the measurement of area, using a single lateral film, is more reliable than simple measurements of length and depth and easier than determination of volume.

a) At birth - 25 sq. mm.
b) Age 10 = 65 sq. mm.
c) Age 15 = 75 sq. mm.

b. Function

1) Gonadotropins

a) The concept has long been held that the secretion of gonadotropins begins about one year prior to puberty and is responsible for the gonadal maturation that, in turn, is responsible for secondary sexual development. This concept received support from such studies as those of Gruelich et al (Soc. Research Child Development 7:43, 1942) in boys wherein before age 12 no gonadotropins were found; between 13 and 14, half had demonstrable activity; after 14, the values increased toward the adult range. There was a closer association with maturity status than with chronological age.

b) But more recent studies question the validity of this concept

1) Fitschen and Clayton (Arch. Dis. Child. 40:16, 1965) found that the marked rise toward adult values occurs well after puberty has begun.

2) Kulin, et al (J. Clin. Endo. 27:1123, August, 1967) found that 17% of urines from normal pre-pubertal children have positive assays; that 75% of such children had at least one positive assay when multiple urines were tested and that no change in the frequency of positive assays was noted in pubertal children. They conclude that "The earliest developments of secondary sexual characteristics appear to be associated with small, if any, increases in total gonadotropin excretion."

c) Using a more sensitive and specific radioimmunoassay, Bagshawe et al (Lancet 1:1118, 1966) did find smaller amounts of LH in the urine of children than in that of adult males. Thus the real significance of gonadotropin secretion in the initiation of puberty may not be known until better techniques for assay are used.

2) Growth hormone

a) The levels of G. H. in children are higher than in adults (Hunter and Greenwood. Biochem. J. 91:43, 1964). A much greater rise was found between meals and at night in children (Hunter and Rigal, J. Endocrin. 34:147, 1966).

b) The rise following insulin-induced hypoglycemia is similar in pre-pubertal boys and girls and comparable to that seen in post-pubertal men and women. (Parker, et al. J. Clin. Endocrinol. 27:1129, August, 1967). The response to arginine was greater in both girls and women than in boys and men.

3) ACTH: There are no known alterations in ACTH secretion before or during adolescence.

4) TSH: The relatively common "simple" goiter of adolescence presumably reflects a physiologically normal increase in secretion of TSH in response to an increased need of the growing organism for thyroid hormone and a relative iodine deficiency.

2. Gonads

a. Testis

1) Size: See below

2) Structure

a) Seminiferous tubules enlarge and spermatogenesis begins

b) Interstitial cells of Leydig differentiate

3) Function

a) Androgen synthesis

(1) Usually measured as urinary 17-Ketosteroids, which remain below 1.5 mg per day until age 9 and rise progressively to adult levels of 8 to 22 mg for boys.

(2) Urinary testosterone shows a similar rise with adult levels reached at age 18 (Knorr. Acta Endocrinol. 54:215, February, 1967).

b) Spermatogenesis: early stages maintained by androgen but FSH needed for final stages.

b. Ovaries

1) Size: Increase in weight from 2 Grams at age 8 to 10 Grams at age 18.

2) Structure: At puberty Graafian follicles mature more completely under influence of FSH. Ovulation with rupture of follicle requires synergism with LH. Regular ovulatory cycles appear about 3 years after menarche.

3) Secretion:

a) Estrogens from Graafian follicle (& adrenal)

(1) Low levels before age 8 with steep rise during puberty

(2) Estrogen effect can be roughly assayed by cytology of vaginal epithelium or urinary sediment.

b) Progesterone from corpus luteum (& adrenal)

(1) Excreted as pregnanediol

(2) Levels rise after ovulation

3. Adrenals: Weight increases from 5 Gms at age 5 to 10 Gms at age 15.

a. Corticoids:

1) Urinary levels (17-Hydroxycorticoids) dependent upon body size (Migeon, et al. Metabolism, 12:718, 1963).

2) Cortisol secretion rate = 12 ± 2.5 mg/sq. meter/24 hours for all ages (Kenny, et al. Pediatrics 37:34, Jan., 1966).

3) Plasma levels - normal adult levels and diurnal variation established by age 3 (Franks, J. Clin. Endocrinol. 27:75, Jan. 1967).

4) Response to ACTH: Absolute value of urinary 17-HOCS rise less than in adults but good response seen (Salmi. Acta paediat. 48 (Supp. 118): 91, 1959).

b. Androgens: in the female, responsible for growth of sexual hair on the pubis and in the axillae, for Seborrhea and acne and possibly for development of the labia majora. Normal adult female 17-Ketosteroid - 5 to 15 mg/day.

c. Aldosterone: When corrected for surface area, the excretion and secretion rates are equivalent to those of adults (New, et al. J. Clin. Invest. 45: 412, March, 1966).

4. Thyroid

a. Size: 6 Grams at age 5, 8 Grams at 10, 15 Grams at 15, 24 Grams at 20.

b. Function:

1) PBI, BEI, T_4 by column are all about 1 ug% lower in adolescent (15 year old) males and about 1.5 ug% lower in 12 year old girls than in pre-pubertal children, probably related to a decreased concentration of thyroid binding prealbumin (Oddie & Fisher. J. Clin. Endo. 27:89, Jan. 1967).

2) Plasma half-life of thyroxine is slightly shorter than in adults (6 days vs 6.7 days, according to Beckers, et al. J. Clin. Endocrinol. 26:202, Feb. 1966).

3) Renal I_2 clearance is increased as is the activity of the thyroid iodine pump (Malvaux, et al. J. Clin. Endocrinol. 25:817, June, 1965). A relative I_2 deficiency may be the mechanism of "adolescent goiter", similar to the mechanism of "pregnancy goiter".

C. Measurements of growth, development and maturity

1. In view of the marked differences in onset and timing of development, criteria other than chronological age are obviously essential. The concept of developmental age or physiological maturity has been useful. The following criteria have been used to assign a developmental age:

a. Skeletal age by X-ray - most commonly used

1) determined by number of ossification centers, their stage of development and the degree of epiphyseal fusion.

2) The left hand and wrist are most commonly used with standards published by Greulich and Pyle (Radiographic Atlas of Skeletal Development of the Hand and Wrist. Second edition. Stanford U. Press, 1959) or Todd (Atlas of Skeletal Maturation - Hand. Mosby, 1937).

3) Though a useful measure, bone age can vary in the same individual between the hand and wrist and other areas and among presumably normal subjects. (Mellman, et al. The diagnostic usefulness of skeletal maturation in an endocrine clinic. Pediatrics 23:530, March, 1959).

4) Variation occurs between competent observers and the consistency of a single observer is only such than two-thirds of duplicate assessments fall within ± 6 months.

5) Specific instances wherein skeletal age is of particular value:

a) Hypothyroidism and hypopituitarism - bone age usually well below height age.

b) Delayed adolescence - bone age usually slightly below height age.

c) Gonadal dysgenesis (Turner's) - bone age usually not delayed whereas height age is.

d) Primary or constitutional short stature - bone age equal to or greater than height age.

e) Excess cortisol - bone age usually delayed to the same degree as height age.

f) Exogenous obesity - usually bone age and height age slightly advanced.

g) Excess androgens (adrenogenital syndrome) - bone age advanced beyond height age.

h) Precocious puberty - bone age and height age equally advanced.

b. Dental age - of value only below age of puberty

c. Morphological age

1) Weight and height of less value as indices of maturity

2) Shape of greater value but more difficult to assess and compare.

d. Secondary sex character age - arbitrary ratings (1 to 5) for development of genitals, pubic hair and breasts. Though there is considerable variation in the onset and timing of development, the sequence is quite uniform. The entire process usually takes 4 to 5 years and girls usually start 2 years before boys. The sequence is diagramed in Figures 1 and 2 on the next to last page.

1) Boys - Criteria based on data of Schonfeld (Am. J. Dis. Child. 65:535, 1943), and Greulich, et al. National Research Council, 1942.

a) Stage 1: Pre-adolescent

(1) Genitalia are of same size and proportions as in early childhood

(a) Penis: 3 to 8 cm. in length, 3 to 5 cm in circumference

(b) Testes: 2 Gms in weight, 0.3 to 1.5 ml in volume, less than 2 cm in length.

(2) No pubic, facial or axillary hair

b) Stage 2: Onset of puberty

(1) Testes enlarge to 2 to 12 ml in volume

(2) Scrotal skin reddens and coarsens

(3) Penis enlarges slightly, if at all

(4) Prostate enlarges but feels monolobar

(5) Pubic hair develops into a conspicuous growth of lightly pigmented, downy hair.

c) Stage 3: Spurt in height, enlargement of larynx

(1) Further growth of testes and scrotum

(2) Penis enlarges: 8 to 15 cm in length, 5 to 10 cm in circumference

(3) Pubic hair - the lightly pigmented downy hair increases in length, coarseness and amount; interspersed are some long, coarse, pigmented hairs which are straighter and finer than adult pubic hair.

(4) In some, a small amount of short, fine facial, axillary and circumanal hair is present.

(5) Gynecomastia obvious in about one-third, though present in all.

d) Stage 4: First ejaculation

(1) Testes, penis, scrotum increased in size.

(2) Pubic hair adult in type but amount and extent limited

(3) Facial and axillary hair slightly more developed. Apocrine sweat glands enlarge.

(4) Prostate - lateral lobes palpable.

e) Stage 5: End of puberty

(1) Genitals reach adult size:

(a) Testes: greater than 3 cm in length, 35 Gm in weight, 8 to 25 ml. in volume.

(b) Penis: 10 to 18 cm. in length, 6 to 10 cm in circumference

(2) Pubic hair adult in quantity and type, but may continue to extend for many years

(3) Facial and axillary hair of more adult type

(4) Gynecomastia disappears

(5) Spurt in muscular strength

2) Girls: The developmental maturity of girls is based on breast size, pubic hair and onset of menses. Ovarian growth presumably precedes these by at least one year.

a) Breast development

(1) Stage 1: Pre-adolescent with only slight elevation of papilla

(2) Stage 2: Breast bud appears as small mound; areola enlarges in diameter

(3) Stage 3: Further enlargement and elevation of breast and areola, with no separation of their contours.

(4) Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast

(5) Stage 5: Mature stage with recession of areola and projection of papilla only.

b) Pubic hair

(1) Stage 1: None

(2) Stage 2: Sparse, slightly pigmented, straight, chiefly along labia

(3) Stage 3: Darker, coarser, more curled

(4) Stage 4: Adult in type but covers smaller area.

(5) Stage 5: Adult in type, quantity and lateral distribution

c) Menarche usually at about Stage 4 and after height spurt.

2. Relationships between different measures of maturity.

   a. Excellent correlation between skeletal and secondary sex character ages; girls skeletally advanced also menstruate early and have early peak in height.

   b. Little evidence concerning dental age.

   c. The graph shown on the last page is a useful device to determine a patient's initial status and response to therapy.

3. Prediction of adult size from size at earlier ages (Tanner, Growth at Adolescence, p. 87).

   a. Excellent correlation between height at any age (beyond 2) and eventual adult height.

   b. Even better to use skeletal age as index of adult size. The best data are those of Bayley, (J. Pediat. 48:187, 1946), given in Table II.

TABLE II

PREDICTION OF ADULT HEIGHT FROM PRESENT HEIGHT IN RELATION TO SKELETAL AGE

Mean percentages of mature height reached at each age in children with skeletal age RETARDED (a year or more behind chronological age), AVERAGE (within a year of chronological age) or ADVANCED (a year or more advanced beyond chronological age). Source: Bayley, J. Pediat. 48:187, 1956).

Chronological Age	BOYS			GIRLS		
	Retarded	Average	Advanced	Retarded	Average	Advanced
10	76	78	80	81	84	88
11	79	81	83	85	88	93
12	82	84	87	88	93	97
13	85	87	91	91	96.5	98
14	88	92	96	95	98	99
15	92	96	98	98	99	99.5
16	96	98	99	99	99.5	100
17	98	99	100	99.5	100	100
18	99	100	100	100	100	100

D. Physical growth at adolescence

1. Variation in different tissues:

Every muscular and skeletal dimension of the body takes part in the adolescent growth spurt. Even the head diameters, practially unchanged since a few years after birth, accelerate somewhat. Only the brain does not change in size. Lymphatic tissue decreases and, in boys, the subcutaneous fat on the limbs decreases. There is a fairly regular oder in which various dimensions accelerate: leg length first, then hip width, chest breadth, shoulder breadth, trunk length and chest depth last. The spurt in height is due more to an increase in length of trunk than length of leg, the ratio of trunk length/leg length always increases during adolescence.

As seen in the lower figure (3) on the next to last page, the peak in weight gain occurs about 6 months after the height peak. The peak in strength gain occurs about 9 months after the weight peak.

2. Variation in different individuals

a. Sex differences

1) Most differences, such as hip and shoulder breadths, arise by differential growth rates operating only at adolescence and are a direct result of the differences in sex hormone secretion.

2) Other differences, such as the overall greater body size and the increase in leg and arm lengths relative to the trunk in males, arise consequent to the later onset of adolescence and the slower maturation of the male. The retardation of the male is presumably caused by genes on the Y chromosome. As seen in the lower figure, the actual peak velocity of growth is almost the same in the two sexes.

3) Still other differences, such as the greater length of the forearm relative to the whole arm in the male, are of unknown cause.

b. Factors affecting rate of growth and age of puberty.

1) The earlier the onset, the faster the rate of growth and the greater the total growth.

2) The taller the child before puberty, the earlier the onset of puberty.

3) Body physique - The muscular (mesomorphs) and fat tend to mature early; the lean and thin (ectomorphs) tend to mature later.

4) Climate - no effect

5) Race - differences exist but may largely reflect nutrition and environment

6) Season of year - growth in height fastest in spring; growth in weight fastest in autumn.

7) Genetic - the fundamental determinant of the rate of development, best seen in studies of age of menarche.

8) Nutrition - poor nutrition as seen during wars and economic depressions delay both the onset and extent of adolescent growth; these effects are less noticable in girls; usually the effects are reversible but permanent stunting can occur with severe malnutrition. The major need appears to be protein (Mitchell, J. Am. Diet. Assoc. 44:165, 1964.

9) Illness - no effect from repeated minor illnesses but definite retardation occurs with major illness; this is usually reversible. Bauer (Helv. paediat. Acta 9:127, 1954) followed 34 nephrotics, normal in size at onset. Their height fell to 70% of normal after 2 years of illness but was back to 94% 18 months after recovery.

10) Psychological factors - probably effective but hard to distinguish from other factors. The striking growth retardation seen in 15 emotionally deprived children reported by Powell, et al (New England J. Med. 276: 1271, June 8, 1967) is the best evidence for such an effect.

11) Intrauterine factors, other than genetic - Warkany, et al (Am. J. Diseases Children 102:127, 1961) report dwarfism and retardation in children born to mothers having had various problems during pregnancy such as e excessive nausea and vomiting, hypertension, poor weight gain, excessive irradiation, rashes, or placental anomalies.

12) Socio-economic and size of family - probably related to nutrition and illness.

13) Secular trend - since 1830, there has been a striking tendency for the time of adolescence, as seen by menarche or the growth spurt, to come earlier and for children to grow bigger. Most of the increase in height occurred in children born between 1900 and 1925.

a) adults are now 4 inches taller than 100 years ago and the menarche is over 3 years earlier.

b) the rate of maturation is also faster, with maximum height now usually reached by age 18 in males and 16 in females, whereas in 1900, the maximum was not reached until age 26.

c. Bakwin (Lancet 2:1195, Dec. 5, 1964) presents data showing that this increase has probably reached an end and strongly suggests it was related to socio-economic factors affecting nutrition, etc.

Abnormalities of Adolescence

A. Precocious sexual development - prior to age 8 in girls and age 10 in boys.

1. Caused by gonadotropin secretion with normal maturation of gonads

a. Neurogenic - brain tumor, encephalitis, hypothalamic disorder, Albright's Syndrome

Albright's Syndrome: Polyostotic fibrous dysplasis with precocious puberty

Case 1. R. B. had been bothered with headaches since age 2 and was said to have suppression amblyopia at age 7 when he was noted to be poorly co-ordinated and to have difficulty with vision. Irregular spotty areas of skin pigmentation present since infancy, had been getting larger. At age 8 1/2, pubic hair and acne were noted and, soon thereafter, the genitals grew considerably.

When seen at age 9, in addition to the precocious development of the testes (3.5 cm in length) and penis, he had multiple cafe-au-lait spots and, on X-ray, 1.5 to 2 cm radiolucent defects in the distal femoral shafts bilaterally. Bone age was 12 1/2.

Comment: Only 3 cases of this syndrome in the male have been reported. The syndrome is probably related to intra-cerebral neurofibromatosis

b. Idiopathic or constitutional - no known organic defect in the hypothalamus or pituitary - the diagnosis in over 75% of sexual precocity, more common in girls, including Lina Medina

1) Skeletal growth occurs early but epiphyses close and child ends up stunted

2) Therapy with medroxyprogesterone acetate, introduced by Kupperman in 1962, has been effective in suppressing gonadotropin secretion and secondary sexual development and probably of value in retarding the acceleration of bone maturation (Schoen, J. Clin. Endocrinol. 26:363, April 1966).

c. Sexual precocity and galactorrhea associated with juvenile hypothyroidism. Three patients reported by Van Wyk and Grumbach (Pediatrics 57:416, 1960) in whom the mechanism of excess gonadotropin secretion was postulated to be a "overflow" stimulation of the pituitary, oversecreting TSH in response to primary hypothyroidism.

2. Caused by sex hormone secretion

a. Gonadal - sex hormones at or above adult level

1) Male - interstitial cell tumor of testis

2) Female - ovarian cysts and tumors

b. Adrenal - elevated 17-KS

1) Male

a) congenital adrenal hyperplasia

(1) Enzymatic defect in cortisol synthesis with compensatory over-production of androgens

(2) Testes remain immature

(3) Elevated urinary pregnanetriol

(4) Effectively treated with cortisone

b) Virilizing adrenal adenoma (rare)

2) Female - feminizing adrenal tumor (rare)

B. Delayed sexual development

1. "Simple" delayed puberty - most common cause, seen in boys more frequently than girls

a. Clinical characteristics

1) usually smaller than average throughout childhood, with 2 to 4 year delay in skeletal development, but they have been growing

2) positive family history occassionally

3) usually find early features of puberty (pubic hair, testicular size); may require observation over a 6 month interval.

4) no impairment in physical or mental ability

b. Treatment

1) none for those below 14 or those showing definite evidence of puberty

2) Chorionic gonadrotropin (APL or Antuitrin-S) 2,000 units twice a week for 8 weeks.

a) no well-controlled studies on value

b) prolonged use of large doses will cause testicular damage and gynecomastia (Maddock and Nelson, J. Clin. Endocrinol. 12:985, 1952).

c) No deterious effect of this dose; Turner, et al. (Fert. & Ster. 15: 24, 1964) found 164 of 178 treated patients to be fertile 1 to 20 years later

d) if no increase in testicular size or signs of puberty noted in 6 months, second course may be tried

3) Testosterone, 200 mgm depot-testosterone enanthate, monthly for 4 to 6 months

a) effect may be more immediate

b) possible deleterious effect on testicular maturation

c. Prognosis without treatment - end result re height gain better than indicated in Table II for boys with small stature and delayed puberty. According to Gallagher and Seltzer (Pediatrics 26:984, 1961) short 14 year olds who have just begun puberty (Stage 2) can be predicted to grow 7 inches; those who are in Stage 3 will grow 6 inches.

2. Hypothalamic lesions - extremely rare

   a. Sexual infantilism with obesity (Froehlich)

      1) frequently used for fat boys with "hidden" or poorly developed genitals, who are perfectly normal

      2) other evidences of hypothalamic disease (diabetes insipidus, growth retardation, etc) should be present

      3) Laurence -Moon-Biedl Syndrome = mental retardation, retinitis pigmentosa, diabetes insipidus, polydactylism and syndactylism

         a) autosomal recessive

         b) variations may be present, particularly the absence of polydactylism

   b. Sexual infantilism without obesity - usually with obvious tumors

3. Pituitary deficiency

   a. Isolated deficiency of gonadotropins

      1) If really an isolated deficiency (i.e. with normal growth hormone), patients usually tall and eunuchoidal

      2) Familial form with anosmia and color blindness (Kallman, et al. Am. J. Mental. Def. 48:203, 1944).

      3) Therapy

         a) Testosterone indefinitely

         b) Chorionic gonadotropin (LH) and human menopausal gonadotropin (FSH) have induced testicular maturation (Lytton & Kase, New England J. Med. 274:1061, May 12, 1966)

   b. Panhypopituitarism (Brasel, et al. Am. J. Med. 38:484, April, 1965; Rabkin and Frantz, Ann. Int. Med. 64:1197, June 1966).

      1) If present since early childhood, the patients are dwarfs with normal body proportions for their chronological age, immature features and premature wrinkling of the facial skin

      2) Though the pattern of hormonal loss can be variable, the usual is growth hormone first, then gonadotropin, ACTH and TSH.

      3) The response of plasma growth hormone to insulin-induced hypoglycemia, or even better, arginine infusion is the most definitive diagnostic procedure (Parker, et al. J. Clin. Endocrinol. 27:1129, August, 1967). The radioimmunoassay can be performed in Dr. Unger's lab.

      4) A number of patients with normal or increased height, normal sellas and, in some, mental retardation have been recently reported. They may have had excessive growth hormone (Zimmerman, et al. Am. J. Med. 42:146, Jan. 1967).

Case II: Panhypopituitarism (probably) with dwarfism

K. L. was first seen in 1858 at age 20. He was described by the Metabolic consultant as "a tiny man with the remarkable appearance of an aged infant. His skin has a waxy, yellowish pallor but there is extensive freckling. The skin is remarkably thin and atrophic and exceedingly dry. Axillary and pubic hair is virtually absent. Remarkably, the penis is comparatively large and even more surprising are the well developed and firm testes."

The exact diagnosis was not established. His bone age was 11 and his I.Q. was 84. He had no urinary gonadotropins, low 17-KS and 17-HOCS excretion with a good response to ACTH, very low thyroid function with no response to TSH. The testicular biopsy was said to reflect prior stimulation but complete absence of spermatogenesis and Leydig cells.

Therapy with cortisone, thyroid and methyl-testosterone was instituted but the patient did not return and apparently died about 2 years later.

4. Primary gonadal disorders - high urinary gonadotropins

   a. Girls - almost 50% with primary amenorrhea have a sex-chromosomal defect (Jacobs, et al. Lancet 1:1183, June 3, 1961).

      1) Gonadal dysgenesis (Turner's) (Ferguson - Smith, J. Med. Genet. 2:65, 1965; Engel and Forbes, Medicine 44:135, 1964).

         a) Clinical characteristics

            (1) Failure of secondary sexual development; 16 cases with spontaneous vaginal bleeding have been reported, probably with mosaicism (Kaufman, Pediatrics 37:26, Jan. 1966).

            (2) Somatic anomalies

               (a) Short stature - usually between 52 and 59 inches tall; the few taller patients are mosaics.

               (b) Webbed neck, low hair line, small chin, shield chest, cubitus valgus, short 4th metacarpal, etc.

         b) Etiology: absence of two normal X chromosomes; usually XO but various abnormalities of the 2nd X and mosaicism are found.

         c) Treatment: Estrogens will usually cause some sexual development and may stimulate growth slightly. The short stature is, however, a genetic defect and probably will not respond to hormones.

      2) Ovarian agenesis, hypoplasia or damage of non-genetic cause.

      3) Testicular feminization, a form of male pseudohermaphroditism

         a) Well-developed females, usually without axillary or pubic hair and amenorrhea, whose gonads are testes and sex chromosomes are XY.

b) Now recognized as due to a falure of tissues to respond to testosterone (French, et al. J. Clin. Endocrinol. 26:493, 1966; Gwinup, et al. Am. J. Med. 41:448, Sept. 1966).

b. Bcys

1) Seminiferous tubular dysgenesis (Klinefelter's) (Zuppinger, et al. Acta endocrinol. Supp. 113, 1967; Becker, et al. Arch. Int. Med. 118:314, Oct. 1966).

a) The only constant finding is small testes (usually less than 1 cm in length).

b) Varying degrees of eunuchoidism, gynecomastia, mental retardation.

c) Most have XXY sex-chromosome composition (positive buccal smear).

d) The presence of 2Y chromocomes has been noted in many with tall stature and criminal behavior (Lancet 1:583, March 12, 1966).

2) Turner's syndrome in the male

a) Almost 100 cases of males with webbing of the neck, short stature, cubitus valgus and hypogonadism. (Chaves-Carballo and Hayles. Mayo Clinic Proc. 41:843, Dec. 1966).

b) Normal sex chromosomes

3) Anorchia or rudimentary testes (Bergada et al. Acta endocrinol. 40:521, 1962).

4) Familial hypogonadism with hypospadias, etc (Bowen et al. Ann. Int. Med. 62:252, Feb. 1965).

5. Congenital adrenal hyperplasia (girls)

a. Though usually recognized in infants, an occassional patient will escape detection until adolescence or the defect may not become manifest until later (Lipsett & Riter. Acta endocrinol. 38:481, 1961).

b. Absent secondary sexual characteristics, excessive hirsutism, muscular development and enlarged clitoris with elevated 17-KS and pregnanetriol.

Case III: <u>Congenital adrenal hyperplasia</u>

G. M. was seen in 1963 at age 21, never having developed secondary sexual characteristics or menstruated. Marked hirsutism required shaving every 2 days. The clitoris was quite large and the internal genitalia infantile. Urinary 17-KS was 33 mg per day, pregnanetriol 25 mg. After 7 days of oral cortisone, 25 mg daily, the 17-KS was 7.4, pregnanetriol 2.2.

On this therapy, she feminized nicely, started menses, got married and has had 2 normal pregnancies.

C. Short Stature

1. Bone diseases: chondrodystrophy, Hurler's syndrome, rickets, osteogenesis imperfecta, etc.

2. Nutritional and metabolic disorders

   a. Celiac disease, cystic fibrosis of pancreas, intestinal disaccharidase deficiency, various causes of malabsorption

   b. Chronic renal disease with acidosis

   c. hepatic diseases, galactosemia, glycogen storage disease.

   d. severe nutritional lack

   e. hypokalemia - reported in about 10 cases with hyperplasia of the juxtaglomerular apparatus, hyperaldosteronism, normal blood pressure (Bartter, et al. Am. J. Med. 33:811, 1962).

   f. chronic anoxemia from cardiac or pulmonary diseases

   g. emotional deprivation (Powell, et al. New England J. Med. 276:1271, June 8, 1967).

   h. Zinc deficiency (?) with iron-deficiency anemia, hepatosplenomegaly and hypogonadism (Prasad, et al. Arch. Int. Med. 111:65, April 1963).

3. Endocrine diseases

   a. Hypothyroidism

      1) Congenital (cretinism) - infantile features and skeletal proportions

         a) Without goiter

            (1) athyrotic: may be caused by placental transmission of maternal thyroid auto-antiboides (Blizzard, et al. New England J. Med. 263:327, 1960.

            (2) ectopic (sublingual) thyroid tissue: may not be completely athyrotic and not recognized until adolescence (McGirr. Arch. Dis. Child. 29:561, 1964).

         b) With goiter

            (1) Congenital enzymatic defects, which may be partial and not recognized until later life (Stanbury, J. B. in The Metabolic Basis of Inherited Disease, ed. by Stanbury, et al. 2nd Ed., McGraw-Hill, 1966).

            (2) Iodine deficiency (endemic cretinism)

      2) Acquired

a) idiopathic (? auto-immune)

b) thyroiditis

c) ingestion of anti-thyroid agent

b. Hypopituitarism

1) Isolated growth hormone deficiency

a) Recently described in midgets with sexual ateliosis, inherited as an autosomal recessive trait, in which body proportions, sexual development and postpartum lactation are normal (Rimoin, et al. Science 152:3729, June 17, 1966).

b) Three siblings with dwarfism and hypoglycemia were found to have abnormally high serum growth hormone levels (Laron, et al. Israel J. Med. Sci. 2:142, March, 1966). The authors postulate the production of an abnormal growth hormone.

2) Panhypopituitarism - sella often tiny (Fisher, Am. J. Roent. 91:996, 1964).

c. Sexual precocity with early epiphyseal fusion

d. Cortisol excess

1) Exogenous: definite but usually reversible stunting with steroid therapy. One study showed that ACTH did not inhibit growth though it controlled the underlying disease (Friedman & Strang. Lancet 2:568, Sept. 10, 1966).

2) Endogenous: Cushing's disease (Schletter, et al. J. Clin. Endocrinol. 27:22, Jan. 1967).

Case IV: Cushing's Syndrome in Adolescence

R. M. is a 15 year old who quit growing at age 9 although he gained about 30 pounds. He had frequent headaches, decreased muscular strength, and nocturia times 3.

B.P. = 130/90, slight plethora of face, definite trunkal obesity, with thin extremities, no striae, immature (pre-pubertal) penis and testes, Gr 2 pubic hair.

Urinary 17-HOCS = 19.7 and 23 mg/day with sub-normal suppression to only 6.2 mg on second day of 0.5 mg Dexamethasone q 6 h. On March 10, 1967, bilateral adrenalectomy was performed and one-half of one of the glands was implanted in his right anterior thigh. At present, on no therapy, his urinary 17-HOCS = 10 mg/day.

4. "Primordial" or genetic dwarfism

a. Familial (pygmies)

1) May be normal other than for size

2) Werner's syndrome: premature aging with cataracts, graying, arteriosclerosis, diabetes (Riley, et al. Ann. Int. Med. 63:285, Aug. 1965).

b. Sporadic (? intrauterine dwarfing)

c. Gonadal dysplasia (Turner's)

d. Autosomal anomalies (Mongolism)

5. Miscellaneous

a. Progeria: similar to Werner's

b. Cockayne's syndrome: microcephaly

D. Tall stature

1. Hyperpituitarism - exceedingly rare

2. Hypogonadism with normal growth hormone

3. Marfan's syndrome

4. Constitutional - no recognizable defect

a. Usually have positive family history

b. If therapy is started early enough (ages 8-10), cyclic estrogen is effective in tall girls. If one waits until age 15, no effect is noted. (Whitelaw, Acta endocrinol. 54:473, 1967).

c. Androgens are effective in prepubertal boys (Whitlaw, et al. Acta endocrinol. 50:317, 1960.

General References

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2. Donovan, B. T. and Vander Werff ten Bosch, J. J. Physiology of Puberty. Williams and Wilkins Co., Baltimore, 1965.

3. Tanner, J. M. Growth at Adolescence. 2nd Edition, Blackwell Publications, Oxford, 1962.

Standards

4. Heald, F. T., et al. Physiology of adolescence. New England J. Med. 268:192, 243, 299 and 361, 1963.

5. Falkner, F. Some physical growth standards for White North American Children. Pediatrics, 29:448 and 467, March, 1962.

6. Bayer, L. M. and N. Bayley. Growth Diagnosis, U. Chicago Press, 1959.

III. Some special problems of adolescence

A. Acne Vulgaris - no cure except for the passage of time

1. Mechanism: very small doses of androgens, systemically or topically, cause great enlargement of the sebaceous glands of the prepubertal male and female; estrogens suppress sebaceous secretions only with unusually high, pharmacologic doses (2.5 to 10 mg), but even large doses are ineffective in blocking the effect of androgen given concomitantly. (Straus, et al. J. Invest. Dermat. 39:139, 1962).

2. Treatment (Pochi & Strauss, Mod. Treat. 2:847, 1965)

a. Local: cleansing, lotions, surgery, intralesional corticosteroids - oftentimes useful and always needed

b. Physical therapy

1) U-V light - may be effective

2) X-ray - effective but potentially carcinogenic (Albright & Adday, J.A.M.A. 199:280, Jan. 23, 1967).

c. Systemic

1) Diet - of little, if any value

2) Antibiotics - unquestionably effective, probably by reducing bacteria which liberate fatty acids, the most irritating component of sebum. Tetracycline, 250 to 500 mg daily.

3) Hormones - systemic estrogens in adequate doses are effective after 2-3 months; used in girls without adequate response to other therapy, but not in boys; same doses and schedule as for birth control

4) Diuretics - occassionally of value with pre-menstrual flare-ups.

5) Vitamin A - of no value

6) Corticosteroids - short courses may be of value as "last resort".

7) New agents

a) Anti-androgen-17a-methyl-B-nortestosterone (Zarate, J. Clin. Endo. 26:1394, 1966)

b) Inhibit cholesterol - Eicosa - 5:8:11:14-tetraynoic acid (Strauss, et al. J. Invest. Derm. 48:492, 1967)

B. Cryptorchidism

1. Many undescended testes are intrinsically damaged, so that descent will not improve their function; an undescended testis suffers no damage before age 10 but thereafter irreversible harm to spermatogenesis begins and is progressive (Charny. J. Urol. 83:697, May 1960).

2. Spontaneous descent apparently occurs at puberty since the incidence of undescended testes is 4.2% pre-pubertally and 0.7% post-pubertally (Johnston, Arch. Dis. Childh. 40:113, 1965). However, those that descend may have been only "high-scrotal" in position and not truly undescended.

3. The results of current therapy are doubtful:

   a. Chorionic gonadotropin probably of no value (Bergstrand. Acta endo. 37:231, 1961)

   b. Charny found no normal testes by biopsy in about 100 surgically treated by orchiopexy

   c. Hortling, et al. (J. Clin. Endo. 27:120, Jan. 1967) found about 1/3 of bilaterally operated patients to be fertile, whereas Gross reported 30 of 38 men operated on for bilateral cryptorchidism between 10 and 12 years of age to be fertile (Postgrad. Med. 34:266, 1963).

C. Menstrual disorders

1. Irregular menses - expected in first few years; oligomenorrhea disappears in only 50% but most have normal fertility.

2. Premenstrual symptoms (Sutherland & Stewart, Lancet 1:1180, June 1965)

   a. Tension with irritability and depression seen in over 50%, usually with some edema and often with pre-menstrual pain

   b. A variety of other symptoms may occur:

      1) constipation, lethargy, dry hair and anorexia

      2) diarrhea, increased energy, insomnia, greasy scalp and increased appetite

      3) acneiform eruption in about 70%

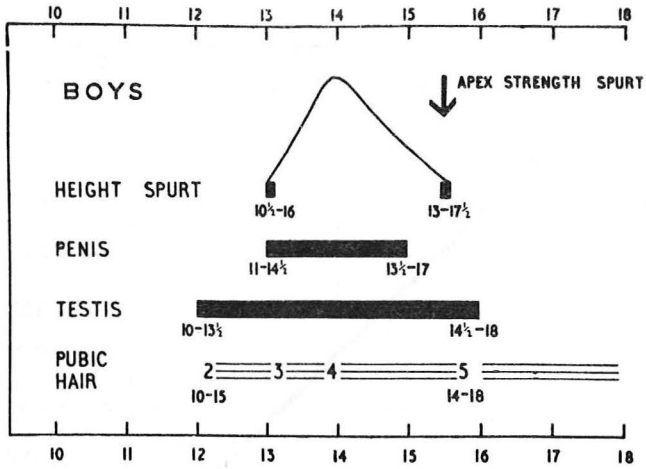
   c. No controlled studies on therapy

D. Slipped capital femoral epiphysis

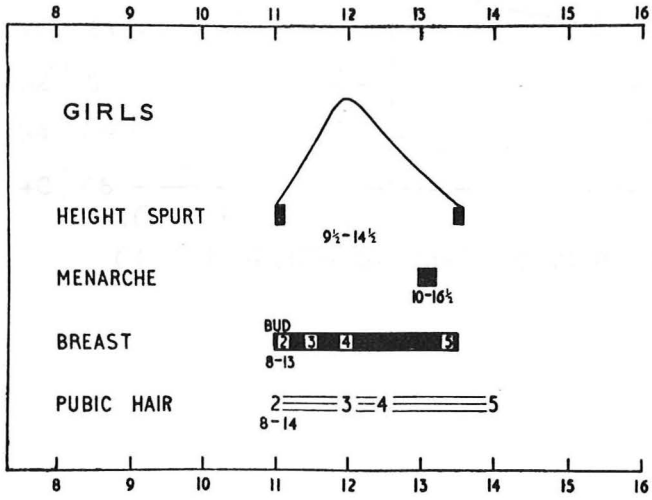
1. A frequent problem, usually seen in large and obese adolescents; 66 patients reported from one hospital (Colwell, Clin. Ortho. 48:89, Sept. 1966).

2. The major problem is failure of recognition causing delay in treatment and poorer results; should be considered in patients with pain in hip, knee or thigh or a limp, particularly after relatively minor trauma.

3. Exam shows decreased flexion, abduction, internal rotation; A-P and lateral films needed to show displacement.



AGE, YEARS



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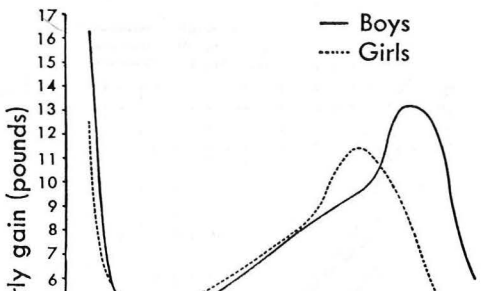

BOYS		GIRLS	
WT (lbs)	HT (in)	WT (lbs)	HT (in)
148	69.5	133	65
142	69	130	65
132	67.5	127	65
119	65	120	64
106	62	110	63
95	60	100	61
86	57	88	58
77	55	78	55
68	53	70	53
61	51	62	51
54	49	54	49
48	46	48	46