Review article

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Some physiological and clinical aspects of puberty*

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Puberty is usually taken to be the process of maturation of the sexually immature child into the sexually mature adolescent, while the term adolescence has been used to describe that period of human development when secondary sex characteristics have appeared completely but full maturity has not been reached. Recently psychologists and child psychiatrists have been using the term adolescence particularly to refer to the emotional and behavioural development and the changes in social interaction during this period of life. In this review we shall use, as Tanner (1962), the words puberty and adolescence without distinction.

This review will emphasize physiological rather than clinical aspects of puberty. Several excellent books and review papers on the subject are available (Tanner, 1962, 1969, 1970; Falkner, 1966; Marshall and Tanner, 1968; Donovan and van der Werff ten Bosch, 1965; van der Werff ten Bosch, 1965; Hubble, 1969; Prader, 1971; Gold and Douvan, 1969), but adolescent medicine has been a long neglected field of medicine on the borderline between paediatrics and internal medicine. It should not be regarded as a new specialty, but be integrated into paediatrics. Studying the anatomy and physiology of adolescence, the paediatrician will gain more insight into the pathology of this period of life, and he will understand better the problems of boys and girls in the period between childhood and adult life.

Sexual maturation and differentiation during adolescence

Maturation of gonadal secretory function and the development of secondary sex characteristics during adolescence are the final phase of a continuous process of sexual differentiation that starts in early

embryonic life. Cytogenetics, experimental embryology and endocrinology, steroid biochemistry, and clinical medicine have contributed to the rapid increase in our knowledge during the past decades. Much of our information has been derived from animal experiments and the results of these experiments very often, but not always, can be applied to the human.

Early differentiation of gonads and genital organs. The structure of the undifferentiated gonad is identical in male (XY) and female (XX) embryos until the 7th week. In the 7th week in the XY-embryo the medullary tissue of the undifferentiated gonad begins to develop in a fetal testis. About two weeks later in the XX-embryo the cellular cortex starts to differentiate in a fetal ovary. Interstitial cells of Leydig are visible at about 8 weeks and it is generally accepted that their secretions are responsible for further male differentiation of genital ducts and external genital organs. The fetal testis acts in three ways: it induces development of the external genital organs, it stimulates differentiation of the Wolffian duct, and it inhibits differentiation of the Müllerian duct. Our knowledge in this field is mainly based on the brilliant animal experiments of Jost (1958). Induction of the development of the external genital organs is an androgenic hormonal effect that can be reproduced by administering testosterone. Physiologically the substance most probably responsible is testosterone, secreted by the Leydig cells of the fetal testis. Jost's experiments have shown that male duct differentiation is promoted by a factor which is secreted by the fetal testis and acts unilaterally. The effect cannot be reproduced by systemic injections of testosterone. For this reason one may argue that the 'duct male organizing substance' is not a common androgenic steroid. However, testosterone secreted by the Leydig cells

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FIG. 1.—Schematic presentation of prenatal sexual differentiation (adapted from Prader, 1971; for explanation see text).

of the fetal testis probably will be present locally (around the testis) in high concentrations which cannot be achieved by systemic injections of testosterone.

Inhibition of the development of the Fallopian tubes and uterus from the Müllerian ducts cannot be accomplished by testosterone. The factor involved is still unknown; it certainly is not an androgen. Fig. 1 summarizes these events. Only the presence of androgens will induce the development of male external genitalia. In the presence of functioning fetal testes the Müllerian ducts involute, while the Wolffian ducts develop (ductus deferens, epididymis, seminal vesicles). In the absence of testes the Wolffian ducts disappear, the Müllerian structures develop (Fallopian tubes, uterus, upper part of vagina). Female development of the genital ducts occurs not only in the presence of an ovary, but also when no gonad is present.

Maturation of gonadal secretory function.

In the male, Leydig cells become inactive a few weeks after birth and change into mesenchymal cells. During childhood the ovary and testis histologically show no signs of activity. However, using sensitive techniques, small amounts of testosterone (Fraser and Horton, 1966; Forest and Migeon, 1970; Degenhart, Visser, and Wilms,

1970), oestradiol (Knorr, Kirschner, and Taylor, 1970), and gonadotropins have been estimated in plasma and urine of prepubertal children. Several authors have reported that prepubertal boys respond to administration of human chorionic gonadotropin (HCG) for 4 to 15 days with an increased excretion of urinary testosterone (Loras, Ollagnon, and Bertrand, 1966), or with an increase in plasma testosterone levels (Saez and Bertrand, 1968; Rivarola, Bergada, and Cullen, 1970). Zachmann and co-workers (1971) have shown recently that even after a single dose of HCG prepubertal boys respond with an increased excretion of urinary testosterone. This procedure can be used to study the function of the testis before puberty. Apparently, mature Leydig cells are not required to produce testosterone in response to HCG.

During recent years several studies have reported values for plasma and urinary gonadotropin concentrations during childhood and pubertal development (Johanson *et al.*, 1969; Raiti *et al.*, 1969; Rifkind *et al.*, 1970; Lee, Midgley, and Jaffe, 1970; Penny *et al.*, 1970), but until very recently little or no information was available on plasma concentrations of gonadotropins and gonadal hormones during the stages of puberty. Grumbach and co-workers (Burr *et al.*, 1970; August, Grumbach,

FIG. 2.—Schematic presentation of changes in plasma LH (luteinizing hormone), FSH (follicle-stimulating hormone), and testosterone during puberty in the male, related to (a) stage of puberty, (b) bone age. Vertical bars indicate periods of greatest changes. Based on data from cross-sectional studies of Burr *et al.* (1970) and August *et al.* (1972). The curves represent our own interpretation of the data.

and Kaplan, 1972; Sizonenko *et al.*, 1970; Jenner *et al.*, 1972) have now published data on plasma concentrations of gonadotropins (FSH, follicle-stimulating hormone, and LH, luteinizing hormone) and gonadal hormones (testosterone, 17β -oestradiol) in relation to pubertal development in the male and female. These results are schematically shown in Fig. 2 and 3. Though such cross-sectional studies

FIG. 3.—Schematic presentation of changes in plasma LH, FSH, and 17β -oestradiol during puberty in the female. Vertical bars indicate periods of greatest changes. Based on data from the cross-sectional study of Jenner *et al.* (1972). The curves represent our own interpretation of the data.

have their well-known limitations and do not necessarily show the sequence of events in individual boys and girls, these data are the best available at this moment and certainly describe the general trend in hormonal events during puberty.

In boys pubertal development apparently starts with an increase in the plasma concentration of luteinizing hormone (LH). There is an increase of testicular volume and an initial rise of plasma testosterone (2nd stage of puberty). Subsequently there is an increase in the plasma concentration of follicle-stimulating hormone (FSH). During the 3rd to 5th stage of puberty there is a gradual increase of both LH and FSH, while a sharp rise in plasma testosterone, associated with further testicular enlargement, takes place during the 3rd to 4th stage of puberty.

Wieland, Yen, and Pohlman (1970) estimating serum LH and testosterone in pooled sera of boys in different age groups also found that an increase of circulating LH precedes an increase in serum testosterone. Animal studies (Woods and Simpson, 1961) and studies on patients with hypogonadotropic hypogonadism (Martin, 1967; Lytton and Kase, 1966) support the concept that the early pubertal enlargement of the testes is due to the effect of LH.

In the female the first hormonal event of puberty is an increased secretion of FSH, though there is also a slight early increase in plasma LH. In their studies on serum gonadotropins in prepubertal girls, Penny *et al.* (1970) found that FSH levels increased at an earlier age (5 to 8 years) than LH levels (9 to 10 years). Fig. 3 shows a continuous increase of both gonadotropins and 17β -oestradiol in relation to stage of puberty. Jenner *et al.* (1972) report good correlation with bone age. Note the remarkably good correlation between hormonal changes and bone age in boys (Fig. 2). Isolated premature development of the breasts (premature thelarche) is usually found in young girls. There are no other signs of sexual maturation; except in some patients minimal oestrinization of the vaginal smear. Growth and bone maturation are normal for age. Jenner *et al.* (1972) reported slightly raised concentrations of plasma oestrogens in some patients. Plasma concentrations of LH and FSH have been found normal (Penny *et al.*, 1970) or somewhat increased (Kennedy *et al.*, 1969; Jenner *et al.*, 1972). These findings indicate increased oestrogen production by the ovaries rather than increased end organ sensitivity as the cause of this condition. Usually the breast enlargement is transient, but it may persist until the onset of puberty at a normal age. It is tempting to speculate that there is early (transient) activation of the hypothalamopituitary-gonadal axis, but if so, the system must be operating at a very low level.

Sexual differentiation of hypothalamus and pituitary. As just discussed, the maturation of gonadal secretory function requires the activity of both gonadotropins, LH and FSH, in both sexes. However, there is a great difference in the secretory pattern of the gonadotropins in the mature adult male and female. In the male plasma concentrations of FSH and LH are relatively constant. In the normal adult female there is a typical cyclic pattern, which is illustrated in Fig. 4. During the first part of the follicular phase (around the 12th day before ovulation) there is a rise in FSH, followed by a decline, and then a rise again, together with a sharp increase of LH at the time of ovulation.

Both values subsequently decrease to low levels. Note the typical increase of plasma oestradiol during the follicular phase, with a peak just before ovulation, and the increase of both oestradiol and progesterone during the luteal phase. Both steroids are secreted by the corpus luteum. Crooke *et al.* (1967) and Crooke, Morell, and Butt (1968) have tried to reproduce this sequence of events in the treatment of infertile patients. They gave a single injection of FSH on day 1, and 9 or 10 days later an injection of chorionic gonadotropin (HCG; this is an LH-like hormone); subsequently ovulation followed.

It has to be emphasized that most adolescent girls after menarche go through a period with irregular, anovulatory cycles. This period of adolescent sterility in the female was noticed long ago, and has been found in many species.

Animal experiments have shown that the control of cyclic release of gonadotropins by the pituitary gland is situated in the hypothalamus. The pituitary gland itself is bipotential: the pituitary of a male adult rat when grafted under the hypothalamus of an adult female rat will be able to release gonadotropins cyclically. In the rat there is a critical period (a few days before birth until 10

FIG. 4.—Schematic presentation of changes in plasma gonadotropins (LH, FSH) and plasma oestradiol and progesterone during a normal menstrual cycle. Based on data from Ross *et al.*, 1970 and Van de Wiele *et al.*, 1970. The curves represent our own interpretation of the data.

FIG. 5.—Cyclic release of gonadotropins in the female. Schematic presentation of the interrelations between hypothalamus (CNS), pituitary gland, and ovary in the female. There is cyclical release of gonadotropins LH and FSH (see Fig. 4). In the rat the 'cyclical release area' is located in the preoptic area of the hypothalamus; this area is 'androgen-sensitive'. The 'tonic release area' is located in the median eminence of the hypothalamus (Barracough and Gorski, 1961). Such areas have not been located in the human. There is feedback regulation between gonad and hypothalamus-pituitary (long-loop system). In the rat, feedback regulation between pituitary and hypothalamus has been proposed (short-loop system); it is not known if this can be applied to the human. FSH-RH and LH-RH: gonadotropin-releasing hormone(s), a decapeptide, whose isolation, structural determination, and synthesis recently has been completed (Schally et al., 1971). Note inhibitory effect on ovulation by some drugs, and regulatory effects of CNS on hypothalamic areas. For further explanation see text.

days after birth) during which the central nervous system becomes sexually differentiated (Pfeiffer, 1936; Barracough and Gorski, 1961; Swanson and van der Werff ten Bosch, 1963, 1964; Harris, 1964; Barracough, 1966). Administration of testosterone to the female rat during this period leads to a 'male type' central nervous system. At adult age ovaries in such animals do not show cyclic variations in activity, but usually develop follicular cysts. Gonadotropin secretion in these animals apparently

is of a noncyclic type. One single injection of 1 μ g testosterone given to the newborn female rat causes sterility at adult age. This effect has been called 'early androgen syndrome'. In experiments using electrical stimulation Barracough and Gorski (1961) localized the androgen-sensitive region in the preoptic area of the hypothalamus. Electrical stimulation of this area causes ovulation in normal female adult rats but not in 'androgen-sterilized' rats. Barracough and Gorski suggest that this area controls cyclical discharge of gonadotropins to cause ovulation. In androgen-treated female animals LH secretion could be induced by electrical stimulation of the median eminence, the ventromedial area of the hypothalamus. According to Barracough and Gorski, this area is responsible for tonic discharge of small amounts of gonadotropin (LH), which maintain oestrogen secretion but cannot independently initiate ovulation. In the male this area is involved in the feedback control of LH-release by circulating androgens. Fig. 5 and 6 schematically represent the interrelations between hypothalamus-pituitary gland and gonads. Though in the human such control areas have not been anatomically localized, the same system of dual hypothalamic control of secretion of gonadotropins is probably operating in the female. There is no

FIG. 6.—Noncyclical release of gonadotropins in the male. Schematic presentation of the interrelations between hypothalamus (CNS), pituitary gland, and testis in the male. See also Fig. 5. In the human the 'tonic release area' probably is located in the median eminence of the hypothalamus. There is feedback-regulation between gonad and hypothalamus-pituitary. For further explanation see text.

evidence that in the human excess of androgens at an early age causes sterility. Female patients treated for congenital adrenal hyperplasia usually have normal ovarian function at adolescence. In some of these patients cystic ovaries have been reported. It is possible that the critical period for 'androgen-sterilization' in the human is at a much earlier period in embryonic life and androgen concentrations required may be higher.

Role of adrenal glands in puberty. During puberty there is increased urinary excretion of 17-ketosteroids in both sexes. Until the age of about 16 years there is no sex difference, afterwards excretion in the male becomes higher than in the female (Knorr, 1965; for a review see Tanner, 1969). This increase in urinary 17-KS excretion in both sexes is mainly due to increased production of adrenal androgens (Visser, 1966; Visser and Degenhart, 1966). A rise in plasma concentrations of dehydroepiandrosterone (DHA) and androsterone in both sexes during puberty has been reported (Migeon *et al.*, 1957; Rosenfield and Eberlein, 1969). The adrenal component of adolescence is under the control of the pituitary gland, since it is absent in the patient with hypopituitarism. It has been postulated that the increased production of adrenal androgens as puberty approaches might be the result of stimulation by a specific pituitary hormone ('androgen-stimulating hormone') which is synergistic with ACTH, but so far this substance has not been isolated. There is no adolescent spurt in the production of cortisol and aldosterone (calculated per m² body surface), and this argues against an increased ACTH stimulation as the primary cause of the adolescent spurt in adrenal androgen production. One might speculate that some factor, possibly a hormone, modifies the response of the adrenal glands to ACTH when puberty starts. However, the fact that in some patients with precocious sexual hair (premature adrenarche), central disorders are found as in patients with true sexual precocity, is in favour of the existence of a specific pituitary 'adrenal androgen stimulating hormone'. Fig. 7 illustrates the interrelations between hypothalamus, pituitary gland, and adrenal cortex.

In children, pubic and axillary hair may develop at an early age without the appearance of the other symptoms of sexual maturation. Bone maturation and height are slightly advanced in most patients. The syndrome is called 'premature adrenarche' or 'pubarche'. It is usually seen in girls. Urinary excretion of 17-ketosteroids is moderately raised due to increased excretion of adrenal androgens

FIG. 7.—Schematic presentation of the interrelations between hypothalamus (CNS), pituitary gland, and adrenal cortex. ACTH-RH = ACTH-releasing hormone. ACTH stimulates production of cortisol, androgens, and, to some extent, aldosterone. There is feedback action of cortisol. For further explanation see text.

(mainly dehydroepiandrosterone (DHA); Visser and Degenhart, 1966). Plasma concentrations of DHA and androsterone are increased in some patients (Conly, Sandberg, and Cleveland, 1967). Plasma gonadotropins are normal (Penny *et al.*, 1970) or low (Kenny *et al.*, 1969). The syndrome must be caused by premature activation of the adrenal cortex, which normally takes place in adolescence; there is increased production of adrenal androgens before the hypothalamo-pituitary-gonadal axis is activated.

Hormonal changes during puberty not only reflect quantitative changes in production of gonadal and adrenal steroids, but also changes in biosynthesis and metabolism of steroids, which are due to maturation and/or activation of enzyme systems. In the bull the ratio of androstenedione and testosterone in spermatic vein blood decreases

during puberty, indicating an increase in 17α -dehydrogenase activity in the testis (Lindner, 1961). Available data do not indicate if such a change occurs in men (Fraser and Horton, 1966; Forest and Migeon, 1970). It is very difficult to differentiate the amounts of steroids produced by gonads and adrenals and, moreover, there is peripheral conversion of androstenedione to testosterone and vice versa (Degenhart *et al.*, 1970). Teller (1967) reported evidence of changes in the metabolism of androgens during puberty.

Timing of puberty. The mechanism of the initiation of puberty is an intriguing problem. The rate of growth and development and the onset of puberty are genetically determined, as is illustrated in the similarity of the growth curves and the small difference in time of puberty between identical twins (Tanner, 1962). There is a good correlation between onset of puberty and menarche of mothers and daughters.

The syndrome of true precocious puberty in young children shows that maturation of gonads and secondary sex characteristics can start at a much earlier age than the usual time of onset of puberty. Experiments with rats have shown that pituitary glands of prepubertal animals when grafted under the hypothalamus of hypophysectomized adults start very soon to function in a normal adult fashion. Testes or ovaries of prepubertal animals when transplanted to castrated adults almost immediately function normally in an adult way (Harris and Jacobsohn, 1952; Harris, 1964; Donovan and van der Werff ten Bosch, 1965). Therefore, the control of puberty must be situated in the hypothalamus or other areas of the central nervous system. Donovan and van der Werff ten Bosch (1956, 1965) and other experimental endocrinologists have shown that in the rat destructive lesions in the anterior and posterior part of the hypothalamus cause precocious puberty. The animal experiments by Barraclough (1966) and others, as discussed in the previous section on sexual differentiation of the hypothalamus, also provide strong evidence for the location of hypothalamic centres controlling the release of gonadotropins before and after puberty. In the human, precocious puberty often is caused by lesions in the posterior part of the hypothalamus.

As mentioned before, in prepubertal children small amounts of gonadotropins and gonadal hormones can be estimated in plasma and urine. In children with gonadal dysgenesis plasma gonadotropin levels are raised compared with normal prepubertal children of the same age (Penny *et al.*, 1970; Jenner *et al.*, 1972). In

infantile rats, removal of the ovaries is followed by an increase in plasma gonadotropins (Donovan and van der Werff ten Bosch, 1965). These and other data suggest that a feedback mechanism between hypothalamus, pituitary, and gonads is operating before puberty (Donovan and van der Werff ten Bosch, 1959, 1965). At the onset of puberty the sensitivity of the hypothalamic feedback-receptor cells is changing; these cells, until that time very sensitive to minute amounts of circulating gonadal hormones, become less sensitive and subsequently greater amounts of gonadotropins are released by the pituitary gland via the increased release of FSH- and LH-releasing hormone by the hypothalamus. This stimulates the maturation of gonadal secretory functions, and plasma concentrations of oestradiol and testosterone increase. Ultimately a feedback-system is re-established, but at another (higher) 'gonadostat' level. This concept is illustrated by

FIG. 8.—Schematic presentation of the change in feedback-sensitivity of the hypothalamus at the onset of puberty. Thickness of arrows denotes amount of hormones or strength of signal from CNS. Note that after completion of puberty, the adult's feedback system is re-established at a higher 'gonadostat' level—see text.

Fig. 8. There is evidence for feedback-regulation of FSH and LH release by oestrogens and progesterone in the adult female. Feedback-regulation of LH release by androgens and of FSH and LH release by oestrogens has been reported in the adult male. See Fig. 4, 5, and 6 (for a review see Odell and Moyer, 1971).

Recently Grumbach and co-workers have provided strong evidence for such a change in feedback-

sensitivity at the onset of puberty in the human (Kulin, Grumbach, and Kaplan, 1969, 1972; Kelch, Kaplan, and Grumbach, 1972). Clomiphene-citrate, an anti-oestrogen with weak oestrogen activity, stimulates gonadotropin release in the adult. The precise mechanism of action is not known, but clomiphene probably acts by competing with steroids (oestrogens?) at hypothalamic receptor sites (Bardin, Ross, and Lipsett, 1967). Kulin *et al.* administered clomiphene-citrate in a dosage of 100 mg/m² per day during 7 days to adult males: urinary excretion of FSH and plasma testosterone concentrations increased. The same dosage given to prepubertal children (boys and girls) apparently suppressed FSH excretion and (in boys) plasma testosterone. Clomiphene suppressed FSH and LH excretion in prepubertal children when given in very small amounts of 0.1–1.0 mg/m² per day. 3 girls in the early stages of sexual maturation were given 100 mg/m² per day for 1 week. In one girl FSH excretion increased, in another FSH excretion decreased, in the third no change was observed. These results can be explained by different sensitivity of the hypothalamic feedback-receptor cells to steroids. Clomiphene has weak oestrogenic activity; apparently in prepubertal children the hypothalamic cells are very sensitive to minute amounts of oestrogens. Failure of clomiphene to raise plasma testosterone levels in prepubertal boys has also been reported by Cathro, Saez, and Bertrand (1969).

In another study (Kelch *et al.*, 1972) the Californian workers have shown that very small amounts of oestrogens (ethinyl oestradiol 2–3 µg/m² per day for 4–7 days) in prepubertal children significantly suppress urinary FSH excretion. During puberty a higher dosage of ethinyl oestradiol was required to lower FSH excretion. These studies provide the first direct data in the human to support the concept that decreased sensitivity of the 'gonadostat' is the initiating factor for the onset of puberty in man.

The factors that cause the change in hypothalamic steroid sensitivity are unknown, but it is very likely that there is a release of inhibition by central nervous system 'input'. For many years the pineal gland was thought to regulate the onset of puberty. Pineal tumours have been found in children with precocious puberty. In animals a pineal gland hormone, melatonin, has been found to inhibit gonadal maturation (Cohen *et al.*, 1964; for a recent review see Axelrod, 1970). The physiological significance for the human is unknown.

The central nervous system 'input' that controls the onset of puberty is in some way related to the maturation of the organism as a whole. There

is a good correlation between the degree of ossification of the skeleton (skeletal maturation) and the onset of puberty. Bone age is one of the criteria for estimating developmental age as opposed to chronological age. Androgens and oestrogens accelerate growth and skeletal maturation. Excess of endogenous and exogenous sex hormones, as in precocious puberty and in the treatment of tall girls and boys, advances growth and skeletal maturation. Pubertal development usually does not start until there is a certain degree of skeletal maturation. Many environmental factors affect body growth, skeletal maturation, and the onset of puberty. Apparently there is a correlation of brain maturation and maturation of the body as a whole. At a certain critical point pubertal development starts. Recently Frisch and Revelle (1969, 1970) have suggested that there is a relation between the onset of puberty and a critical body weight. Early and late maturing girls have menarche at the same weight (about 48 kg), but height is different. Frisch and Revelle propose that at a critical body weight metabolic rate is changing, which alters the feedback sensitivity at the hypothalamic level. Some relation between body weight and onset of puberty has been found in the rat (Kennedy and Mitra, 1963).

During the past century in the industrial countries a constant trend toward earlier maturation and earlier onset of puberty in children has been observed (secular trend; for a review see Tanner, 1962, 1969). Children of all ages have been growing taller and heavier; this process starts in infancy (Thomson, 1954), and probably already before birth. The onset of puberty has become earlier at a rate of about 1 year per 25 calendar years. Many factors such as socioeconomic class, illness, and nutrition affect the rate of growth and the onset of puberty. In poor social classes the onset of puberty is later. Children with many sibs may grow less fast than children in small families.

Animal experiments support these findings in the human. Rats nursed in small litters grow faster and reach sexual maturity earlier than rats nursed in large litters (Kennedy and Mitra, 1963). There is evidence that acceleration of growth is connected with earlier maturation of the brain (Lát, Widdowson, and McCance, 1960). During recent years many investigations have shown the lasting effect of undernutrition at early age on body growth and brain development (see for instance Winick, 1968, 1969; Barnes *et al.*, 1968; Stoch and Smythe, 1968; Smart and Dobbing, 1971; Dobbing, 1972). The causes of the trend toward earlier maturity are not clear, but it is well

accepted that better nutrition is one of the most important factors. The effect of better nutrition starts in early life, during the intrauterine period and infancy. It is tempting to speculate that in the human, as in animals, there is a critical period during which environmental factors affect brain development, body growth, and timing of puberty. In the human this period probably occupies the last part of prenatal life and some period (1 to 2 years) after birth.

In summary, the rate of growth and development and the time of onset of puberty are determined by genetic and environmental factors. Normally puberty starts at a critical stage of general development and brain maturation. The 'trigger' might be the attainment of a critical body size. The continuous trend toward earlier maturation and onset of puberty in the industrialized countries can be explained by the constant improvement of environmental conditions at an early age.

From the foregoing discussion it will be evident that it is difficult to define the term 'early' or 'precocious' puberty. One has to consider the great individual variation in the age at which puberty begins and the phenomenon of continuous earlier maturation during childhood. In the industrialized countries the onset of puberty in girls earlier than 8 years of age and in boys earlier than 10 years of age could be defined as precocious puberty. Signs of puberty in such children require extensive investigations and a careful long-term follow-up. In more than 90% in girls and about 50% in boys, precocious puberty is caused by idiopathic early activation of the hypothalamo pituitary-gonadal axis. No direct causal factor can be found. Radioimmunoassay methods for the estimation of plasma gonadotropins are now available and this is most important for the differentiation between 'true' and 'pseudo' precocious puberty. Medical treatment, with the intention of interfering with the abnormal secretion of gonadotropins and/or gonadal hormones and of stopping the most undesirable effects on growth and bone maturation, has been unsuccessful. Medroxyprogesterone acetate (Depo-Provera) probably suppresses the pituitary release of gonadotropins. Menstrual bleeding usually stops. There is certainly some effect on several male and female secondary sex characteristics. It is very difficult to evaluate the effect on bone maturation and ultimate height, but results so far have been disappointing. Unfortunately the drug has some inhibitory effect on the pituitary-adrenal axis (Mathews, Abrams, and Morishima, 1970; Sadeghi-Nejad, Kaplan, and Grumbach, 1971). Apart from medical treatment, children with precocious

puberty and their families usually need careful attention of the child psychologist, child psychiatrist, and social worker. For an extensive review of precocious puberty the reader is referred to van der Werff ten Bosch (1969) and Prader (1971).

Somatic and psychic maturation during adolescence

Adolescent growth spurt and secondary sex characteristics. There are many somatic changes during puberty and most of these are different in both sexes. Boys and girls are different before puberty, but during puberty the differences become much greater. There is growth of the gonads and genitalia; appearance of secondary sex characteristics; a remarkable increase in body growth—body size and body shape (the adolescent growth spurt)—and there are great changes in body composition. These somatic changes during adolescence have been reviewed in great detail by Tanner (1962, 1969). The Table summarizes mean ages for girls and boys when different stages of pubertal development are reached, as reported by several authors (Reynolds and Wines, 1948, 1951; Nicolson and Hanley, 1953; Van Wieringen *et al.*, 1968; Marshall and Tanner, 1969, 1970). The peak of the adolescent growth spurt in height is reached in the average girl at stage B₃ and PH₃, and in the average boy at stage G₄ and PH₄.

The relation between the growth spurt and hormonal changes during puberty is still not clear. Testosterone in boys and oestrogens in girls stimulate growth. The difference in growth spurt between boys and girls is probably due to testosterone. Adrenal androgens probably do not play an important role; in patients with premature adrenarche there is usually only a small increase in height and skeletal maturation. The role of growth hormone may be important. Androgens and oestrogens enhance the release of growth hormone in response to insulin-induced hypoglycaemia. In male patients with delayed puberty and anorchia, treatment with androgens led to higher plasma growth hormone concentrations (Deller, Plunket, and Forsham, 1966; Martin, Clark, and Connor, 1968; Illig and Prader, 1970). Kaplan, Frasier, and Costin (1969) reported a high plasma growth hormone response to hypoglycaemia in children with precocious puberty.

Epiphyseal closure at the end of the growth spurt is probably caused by testosterone and oestrogens. Treatment of tall boys with testosterone and tall girls with oestrogens is followed by

TABLE

Mean ages (yr) for girls and boys at which different stages of pubertal development are reached. Stages of development of genitalia (G2–G5), breasts (B2–B5), and pubic hair (PH₂–PH₅) as described by Tanner (1962, 1969)

	B ₂	B ₃	B ₄	B ₅	PH ₂	PH ₃	PH ₄	PH ₅	Menarche	Country
Girls										
Reynolds and Wines (1948)	10.8	11.4	12.2	13.7	11.0	11.9	12.5	13.9	12.9	U.S.A.
Nicolson and Hanley (1953)	10.6	11.2	—	13.9	11.6	12.5	13.2	—	12.8	U.S.A.
Van Wieringen <i>et al.</i> (1968)	11.0	12.1	13.4	15.2	11.3	12.2	13.3	14.9	13.4	The Netherlands
Marshall and Tanner (1969)	11.2	12.2	13.1	15.3	11.7	12.4	13.0	14.4	13.5	England
Boys										
Reynolds and Wines (1951)	11.5	12.7	13.4	17.3	12.2	13.3	13.9	16.1	—	U.S.A.
Nicolson and Hanley (1953)	11.8	13.1	13.8	15.2	—	—	—	—	—	U.S.A.
Van Wieringen <i>et al.</i> (1968)	11.0	13.2	14.2	15.9	11.8	13.5	14.4	16.0	—	The Netherlands
Marshall and Tanner (1970)	11.6	12.9	13.8	14.9	13.4	13.9	14.4	15.1	—	England

closure of the epiphyses. It is possible that other hormones, such as growth hormone, are involved.

Ossification of the skeleton, as measured by skeletal maturity, is advanced in girls over boys. At birth girls are already some weeks ahead of boys in bone age, and there is a gradual increase until the onset of puberty when the difference has increased to about 2 years. In general, girls enter puberty about 2 years earlier than boys, and as a consequence boys grow for a longer time than girls. This is partly responsible for some somatic differences between the sexes, such as greater adult height and longer limbs in the male. Tanner *et al.* (1959) found that bone age in XO-karyotype children before puberty was not different from normal XX-females; XXY-boys had the same bone age as XY-boys. Thus, the relative retardation of maturation in boys is apparently connected with the presence of the Y-chromosome. Precocious puberty is more often seen in girls than in boys, while delayed puberty is usually seen in boys. In these boys with constitutional delay of growth and puberty, bone age usually is retarded compared with chronological age; there is no evidence for hormonal disorders. The explanation of the advanced skeletal maturation and earlier onset of puberty in girls remains obscure.

Changes in body composition during adolescence. Changes in body composition during adolescence are most impressive (for a review see Owen and Brozek, 1966). Using radiographic and anthropometric methods, changes in bone, muscle, and fat diameters can be measured. There is a spurt in muscle and bone diameters

during adolescence, particularly of the limbs (Tanner, 1965). This is usually accompanied by fat loss in boys, but not in girls. Total body fat and lean body mass have been estimated in adolescents using K⁴⁰ measurements in a 'whole body counter'. Fig. 9 schematically presents the results of Forbes (1963, 1964, 1965), Forbes and Hursh (1963), and Allen, Anderson, and Langham (1960).

FIG. 9.—Schematic curves illustrating the changes in body composition (total body fat and total lean body mass) during adolescence. Based on data from Forbes, 1963, 1964, 1965; Allen *et al.*, 1960; Anderson, 1963. Curves represent our own interpretation of the data and illustrate the general trend in changes. There is great individual variation.

During puberty there is a sharp increase in lean body mass in both sexes. In the female this increase in lean body mass starts about 2 years earlier than in boys and is accompanied by a gradual increase in total body fat. In the male there is an initial decrease in body fat, followed by a gradual increase. These findings confirm the clinical impression of the relatively fat prepubertal boy who changes during puberty to a slender adolescent. Maximal values for lean body mass are reached earlier in the female. At age 18 the male : female ratio for lean body mass is greater than that for weight or height (Forbes, 1965). This explains differences in performance in athletics and other sports between both sexes.

As Forbes (1964, 1965) clearly points out, these changes in body composition during adolescence have important nutritional implications. Nutritional daily requirements for growth purposes alone are considerable and different for both sexes.

Psychic maturation during adolescence. Adolescence is not only characterized by great and rapid somatic changes connected with the process of sexual maturation, but adolescent development also comprises a most important process of psychic maturation. There are qualitative and quantitative changes in the sexual drive, which affect the behaviour of the adolescent. The adolescent is slowly changing his role of dependent child to that of the independent, autonomous adult. There is a shift in personal relationships and a search for identity, while social interactions are changing. There is a continuous increase of intellectual performance, which probably reaches its maximum in the early 20's, after the adolescent years. Abstract thinking develops, which explains the interest of the adolescent in philosophical, ethical, and religious issues.

There is no good evidence for an adolescent growth spurt in intellectual functions. A slight difference in results of intellectual performance tests has been found in relation to physical maturation. Children who are physically advanced for their age score better results than children who are less mature. At a later age such differences probably disappear. Remarkably few data are available. In children with precocious puberty psychological and behavioural maturation usually is not clearly advanced and is related to chronological age.

Some behavioural tests, for instance on interests and social attitudes, also show differences between early and late maturers, and between girls and boys. It should be emphasized that cultural and other

environmental factors may play a more important role than biological factors. The social-cultural climate of the young age group in our modern western society, with its emphasis on sex and competition, can be a great strain for children with the syndrome of short stature and delayed puberty. Psychotherapy and (in boys) carefully controlled intermittent treatment with anabolic steroids may be helpful.

It is not my intention to discuss the aspects of psychic maturation during adolescence in detail. The interested reader is referred to Tanner (1962) and Gold and Douvan (1969). The paediatrician should be aware of the psychological aspects of adolescent development. His understanding can be of immense help to parents, teachers, and adolescents themselves. It is my impression, and I am supported by child psychologists and child psychiatrists, that the dramatic present-day presentation of adolescent problems, as expressed by such phrases as 'rebellious youth' and 'generation-conflict' is largely exaggerated. Mass media over-emphasize the admittedly important problem of minority groups of adolescents. Most adolescents, I believe, are willing to respect their parents' standards and to rely on their judgement and guidance. While slowly finding their way to autonomy, the adolescents' ties to parents and family are more intense than we usually think. Adults have to learn and to understand the physiology of adolescence and have to provide optimal conditions for the growth and development of their children during this period of life. It is certain that the 'facts of nature' present some specific problems: great individual variation in chronological age when puberty starts, advanced maturation in girls as compared with boys, and the trend toward accelerated growth and maturation and earlier onset of puberty but at the same time extension of the period of learning and dependency.

It was with a deep sense of appreciation that I accepted the honour of addressing the British Paediatric Association and the Scottish Paediatric Society by giving the Windermere Lecture. Most of the work which I have reviewed here has been carried out by my fellow human biologists and only a fraction by myself and my co-workers. I am particularly grateful to Professor Van der Werff ten Bosch (Department of Endocrinology, Growth and Reproduction, Medical Faculty, Rotterdam) for help, and Professor Grumbach (Department of Pediatrics, University of California, San Francisco) for sending me unpublished work of his group and giving permission to discuss it here.

REFERENCES

- Allen, T. H., Anderson, E. C., and Langham, W. H. (1960). Total body potassium and gross body composition in relation to age. *Journal of Gerontology*, 15, 348.

- Anderson, E. C. (1963). Three-component body composition analysis based on potassium and water determinations. *Annals of the New York Academy of Sciences*, **110**, 189.
- August, G. P., Grumbach, M. M., and Kaplan, S. L. (1972). Hormonal changes in puberty. III. Correlation of plasma testosterone, LH, FSH, testicular size, and bone age with male pubertal development. *Journal of Clinical Endocrinology and Metabolism*, **34**, 319.
- Axelrod, J. (1970). The pineal gland. *Endeavour*, **29**, 144.
- Bardin, C. W., Ross, G. T., and Lipsett, M. B. (1967). Site of action of clomiphene citrate in men: a study of the pituitary-Leydig cell axis. *Journal of Clinical Endocrinology and Metabolism*, **27**, 1558.
- Barnes, R. H., Moore, A. U., Reid, I. M., and Pond, W. G. (1968). Effect of food deprivation on behavioural patterns. In *Malnutrition, Learning, and Behavior*, p. 203. Ed. by N. S. Scrimshaw and J. E. Gordon. Massachusetts Institute of Technology, Cambridge.
- Barracrough, C. A. (1966). Modifications in the CNS regulation of reproduction after the exposure of prepubertal rats to steroid hormones. *Recent Progress in Hormone Research*, **22**, 503.
- Barracrough, C. A., and Gorski, R. A. (1961). Evidence that the hypothalamus is responsible for androgen-induced sterility in the female rat. *Endocrinology*, **68**, 68.
- Burr, I. M., Sizonenko, P. C., Kaplan, S. L., and Grumbach, M. M. (1970). Hormonal changes in puberty. I. Correlation of serum luteinizing hormone and follicle stimulating hormone with stages of puberty, testicular size, and bone age in normal boys. *Pediatric Research*, **4**, 25.
- Cathro, D. M., Saez, J. M., and Bertrand, J. (1969). The effect of clomiphene on the plasma androgens of pubertal and prepubertal boys. *Acta Endocrinologica (København)*, Suppl. 138, Abst. No. 204.
- Cohen, R. A., Wurtman, R. J., Axelrod, J., and Snyder, S. H. (1964). Some clinical, biochemical, and physiological actions of the pineal gland. *Annals of Internal Medicine*, **61**, 1144.
- Conly, P. W., Sandberg, D. H., and Cleveland, W. W. (1967). Steroid metabolism in premature pubarche and virilizing adrenal hyperplasia. *Journal of Pediatrics*, **71**, 506.
- Crooke, A. C., Butt, W. R., Bertrand, P. V., and Morris, R. (1967). Treatment of infertility and secondary amenorrhoea with follicle-stimulating hormone and chorionic gonadotrophin. *Lancet*, **2**, 636.
- Crooke, A. C., Morell, M., and Butt, W. R. (1968). The recovery of exogenous follicle stimulating hormone from urine. In *Gonadotropins*. Ed. by E. Rosenberg. Geron-X, Los Altos, California.
- Degenhart, H. J., Visser, H. K. A., and Wilmsink, R. (1970). Excretion and production of testosterone in normal children, in children with congenital adrenal hyperplasia, and in children with precocious puberty. *Pediatric Research*, **4**, 309.
- Deller, J. J., Plunket, D. C., and Forsham, P. H. (1966). Growth hormone studies in growth retardation. Therapeutic response to administration of androgen. *California Medicine*, **104**, 359.
- Dobbing, J. (1972). Undernutrition and the developing brain. The use of animal models to elucidate the human problem. In *Normal and Abnormal Development of Brain and Behaviour*, p. 20. Ed. by G. B. A. Stoelting and J. J. van der Werff ten Bosch. Boerhaave series for postgraduate medical education, Leiden University Press, Leiden.
- Donovan, B. T., and Werff ten Bosch, J. J. van der (1956). Precocious puberty in rats with hypothalamic lesions. *Nature (London)*, **178**, 745.
- Donovan, B. T., and Werff ten Bosch, J. J. van der (1959). The hypothalamus and sexual maturation in the rat. *Journal of Physiology*, **147**, 78.
- Donovan, B. T., and Werff ten Bosch, J. J. van der (1965). *Physiology of Puberty*. Arnold, London.
- Falkner, F. T. (Editor) (1966). *Human Development*. Saunders, Philadelphia and London.
- Forbes, G. B. (1963). Nutritional implications of the whole body counter. *Nutrition Reviews*, **21**, 321 (correction in *Nutrition Reviews*, 1964, 22, 96).
- Forbes, G. B. (1964). Growth of the lean body mass during childhood and adolescence. *Journal of Pediatrics*, **64**, 822.
- Forbes, G. B. (1965). Toward a new dimension in human growth. *Pediatrics*, **36**, 825.
- Forbes, G. B., and Hursh, J. B. (1963). Age and sex trends in lean body mass calculated from K⁴⁰ measurements. *Annals of the New York Academy of Sciences*, **110**, 255.
- Forest, M. G., and Migeon, C. J. (1970). Percentage of testosterone, androstenedione, and dehydroisoandrosterone bound to plasma protein in preadolescent children. *Journal of Pediatrics*, **76**, 732.
- Frasier, S. D., and Horton, R. (1966). Androgens in the peripheral plasma of prepubertal children and adults. *Steroids*, **8**, 777.
- Frisch, R. E., and Revelle, R. (1969). The height and weight of adolescent boys and girls at the time of peak velocity of growth in height and weight: longitudinal data. *Human Biology*, **41**, 536.
- Frisch, R. E., and Revelle, R. (1970). Height and weight at menarche and a hypothesis of critical body weights and adolescent events. *Science*, **169**, 397.
- Gold, M. G., and Douvan, E. M. (1969). *Adolescent Development, Readings in Research and Theory*. Allyn and Bacon, Boston.
- Harris, G. W. (1964). Sex hormones, brain development and brain function. *Endocrinology*, **75**, 627.
- Harris, G. W., and Jacobsohn, D. (1952). Functional grafts of the anterior pituitary gland. *Proceedings of the Royal Society. Series B. Biological Sciences*, **139**, 263.
- Hubble, D. V. (1969). *Paediatric Endocrinology*. Blackwell, Oxford.
- Illig, R., and Prader, A. (1970). Effect of testosterone on growth hormone secretion in patients with anorchia and delayed puberty. *Journal of Clinical Endocrinology and Metabolism*, **30**, 615.
- Jenner, M. R., Kelch, R. P., Kaplan, S. L., and Grumbach, M. M. (1972). Hormonal changes in puberty. IV. Plasma estradiol, LH, and FSH in prepubertal children, pubertal females, and in precocious puberty, premature thelarche, hypogonadism, and in a child with a feminizing ovarian tumor. *Journal of Clinical Endocrinology and Metabolism*, **34**, 521.
- Johanson, A. J., Guyda, H., Light, C., Migeon, C. J., and Blizzard, R. M. (1969). Serum luteinizing hormone by radioimmunoassay in normal children. *Journal of Pediatrics*, **74**, 416.
- Jost, A. (1958). Embryonic sexual differentiation (morphology, physiology, abnormalities). In *Hermaphroditism, Genital Anomalies and Related Endocrine Disorders*, p. 15. Ed. by H. W. Jones and W. W. Scott. Williams and Wilkins, Baltimore.
- Kaplan, S. A., Frasier, S. D., and Costin, G. (1969). Growth hormone secretion in idiopathic precocious puberty: Effect of medroxy-progesterone. *Journal of Pediatrics*, **75**, 133.
- Kelch, R. P., Kaplan, S. L., and Grumbach, M. M. (1972). Suppression of urinary and plasma gonadotropins by exogenous estrogens in prepubertal and pubertal children. American Pediatric Society, Washington, May 1972. (Abst.) *Pediatric Research*, **6**, 354.
- Kennedy, G. C., and Mitra, J. (1963). Body weight and food intake as initiating factors for puberty in the rat. *Journal of Physiology*, **166**, 408.
- Kenny, F. M., Midgley, A. R., Jr., Jaffe, R. B., Garces, L. Y., Vasquez, A., and Taylor, F. H. (1969). Radioimmunoassayable serum LH and FSH in girls with sexual precocity, premature thelarche and adrenarche. *Journal of Clinical Endocrinology and Metabolism*, **29**, 1272.
- Knorr, D. (1965). Untersuchungen zur Altersabhängigkeit der Ausscheidung einzelner chromatografisch getrennter Steroide während des Kindes- und Reifungsalters. In *Fortschritte der Paedologie*, p. 109. Ed. by F. Linneweh. Springer, Berlin.
- Knorr, D. W. R., Kirschner, M. A., and Taylor, J. P. (1970). Estimation of estrone and estradiol in low level urines using electroncapture gas-liquid chromatography. *Journal of Clinical Endocrinology and Metabolism*, **31**, 409.
- Kulin, H. E., Grumbach, M. M., and Kaplan, S. L. (1969). Changing sensitivity of pubertal gonadal hypothalamic feedback mechanism in man. *Science*, **166**, 1012.
- Kulin, H. E., Grumbach, M. M., and Kaplan, S. L. (1972). Gonadal-hypothalamic interaction in prepubertal and pubertal man: effect of clomiphene citrate on urinary FSH and LH and plasma testosterone. *Pediatric Research*, **6**, 162.
- Lät, J., Widdowson, E. M., and McCance, R. A. (1960). Some effects of accelerating growth. III. Behaviour and nervous activity. *Proceedings of the Royal Society. Series B. Biological Sciences*, **153**, 347.

- Lee, P. A., Midgley, A. R., Jr., and Jaffe, R. B. (1970). Regulation of human gonadotropins. VI. Serum follicle stimulating and luteinizing hormone determinations in children. *Journal of Clinical Endocrinology and Metabolism*, **31**, 248.
- Lindner, H. R. (1961). Androgens and related compounds in the spermatic vein blood of domestic animals. II. Species-linked differences in the metabolism of adrostenedione in blood. *Journal of Endocrinology*, **21**, 161.
- Loras, B., Ollagnon, C., and Bertrand, J. (1966). Dosage de la testostérone urinaire chez le garçon normal durant la seconde enfance et au cours de la puberté. Action de la gonadotrophine chorionique. *Pédiatrie*, **21**, 455.
- Lytton, B., and Kase, N. (1966). Effects of human menopausal gonadotrophin on a eunuchoid male. *New England Journal of Medicine*, **274**, 1061.
- Marshall, W. A., and Tanner, J. M. (1968). Growth and physiological development during adolescence. *Annual Review of Medicine*, **19**, 283.
- Marshall, W. A., and Tanner, J. M. (1969). Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, **44**, 291.
- Marshall, W. A., and Tanner, J. M. (1970). Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood*, **45**, 13.
- Martin, F. I. R. (1967). The stimulation and prolonged maintenance of spermatogenesis by human pituitary gonadotrophins in a patient with hypogonadotrophic hypogonadism. *Journal of Endocrinology*, **38**, 431.
- Martin, L. G., Clark, J. W., and Connor, T. B. (1968). Growth hormone secretion enhanced by androgens. *Journal of Clinical Endocrinology and Metabolism*, **28**, 425.
- Mathews, J. H., Abrams, C. A. L., and Morishima, A. (1970). Pituitary-adrenal function in ten patients receiving medroxyprogesterone acetate for true precocious puberty. *Journal of Clinical Endocrinology and Metabolism*, **30**, 653.
- Migeon, C. J., Keller, A. R., Lawrence, B., and Shepard, T. H. II. (1957). Dehydroepiandrosterone and androsterone levels in human plasma. Effect of age and sex; day-to-day and diurnal variations. *Journal of Clinical Endocrinology and Metabolism*, **17**, 1051.
- Nicolson, A. B., and Hanley, C. (1953). Indices of physiological maturity, derivation and interrelationships. *Child Development*, **24**, 3.
- Odell, W. D., and Moyer, D. L. (1971). *Physiology of Reproduction*. Mosby, Saint Louis.
- Owen, G. M., and Brozek, J. (1966). Influence of age, sex and nutrition on body composition during childhood and adolescence. In *Human Development*, p. 222. Ed. by F. Falkner. Saunders, Philadelphia and London.
- Penny, R., Guyda, H. J., Baghdassarian, A., Johanson, A. J., and Blizzard, R. M. (1970). Correlation of serum follicular stimulating hormone (FSH) and luteinizing hormone (LH) as measured by radioimmunoassay in disorders of sexual development. *Journal of Clinical Investigation*, **49**, 1847.
- Pfeiffer, C. A. (1936). Sexual differences of the hypophyses and their determination by the gonads. *American Journal of Anatomy*, **58**, 195.
- Prader, A. (1971). Pubertät. In *Klinik der inneren Sekretion*, p. 1067. Ed. by A. Labhart. Springer, Berlin.
- Raiti, S., Johanson, A., Light, C., Migeon, C. J., and Blizzard, R. M. (1969). Measurement of immunologically reactive follicle stimulating hormone in serum of normal male children and adults. *Metabolism*, **18**, 234.
- Reynolds, E. L., and Wines, J. V. (1948). Individual differences in physical changes associated with adolescence in girls. *American Journal of Diseases of Children*, **75**, 329.
- Reynolds, E. L., and Wines, J. V. (1951). Physical changes associated with adolescence in boys. *American Journal of Diseases of Children*, **82**, 529.
- Rifkind, A. B., Kulin, H. E., Rayford, P. L., Cargille, C. M., and Ross, G. T. (1970). 24-hour urinary luteinizing hormone (LH) and follicle stimulating hormone (FSH) excretion in normal children. *Journal of Clinical Endocrinology and Metabolism*, **31**, 517.
- Rivarola, M. A., Bergada, C., and Cullen, M. (1970). HCG stimulation test in prepubertal boys with cryptorchidism, in bilateral anorchia and in male pseudohermaphroditism. *Journal of Clinical Endocrinology and Metabolism*, **31**, 526.
- Rosenfield, R. L., and Eberlein, W. R. (1969). Plasma 17-ketosteroid levels during adolescence. *Journal of Pediatrics*, **74**, 932.
- Ross, G. T., Cargille, C. M., Lipsett, M. B., Rayford, P. L., Marshall, J. R., Strott, C. A., and Rodbard, D. (1970). Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles. *Recent Progress in Hormone Research*, **28**, 1.
- Sadeghi-Nejad, A., Kaplan, S. L., and Grumbach, M. M. (1971). The effect of medroxyprogesterone acetate on adrenocortical function in children with precocious puberty. *Journal of Pediatrics*, **78**, 616.
- Saez, J. M., and Bertrand, J. (1968). Studies on testicular function in children: plasma concentrations of testosterone, dehydroepiandrosterone and its sulfate before and after stimulation with human chorionic gonadotrophin. *Steroids*, **12**, 749.
- Schally, A. V., Arimura, A., Kastin, A. J., Matsuo, H., Baba, Y., Redding, T. W., Nair, R. M. G., Debeljuk, L., and White, W. F. (1971). Gonadotropin-releasing hormone: one polypeptide regulates secretion of luteinizing and follicle-stimulating hormones. *Science*, **173**, 1036.
- Sizonenko, P. C., Burr, I. M., Kaplan, S. L., and Grumbach, M. M. (1970). Hormonal changes in puberty. II. Correlation of serum luteinizing hormone and follicle stimulating hormone with stages of puberty and bone age in normal girls. *Pediatric Research*, **4**, 36.
- Smart, J. L., and Dobbing, J. (1971). Vulnerability of developing brain. II. Effects of early nutritional deprivation on reflex ontogeny and development of behaviour in the rat. *Brain Research*, **28**, 85.
- Stoch, M. B., and Smythe, P. M. (1968). Undernutrition during infancy, and subsequent brain growth and intellectual development. In *Malnutrition, Learning, and Behavior*, p. 278. Ed. by N. S. Scrimshaw and J. E. Gordon. Massachusetts Institute of Technology, Cambridge.
- Swanson, H. E., and Werff ten Bosch, J. J. van der (1963). Sex differences in growth of rats, and their modification by a single injection of testosterone propionate shortly after birth. *Journal of Endocrinology*, **26**, 197.
- Swanson, H. E., and Werff ten Bosch, J. J. van der (1964). The 'early-androgen' syndrome; differences in response to pre-natal and post-natal administration of various doses of testosterone propionate in female and male rats. *Acta Endocrinologica (København)*, **47**, 37.
- Tanner, J. M. (1962). *Growth at Adolescence*, 2nd ed. Blackwell, Oxford.
- Tanner, J. M. (1965). Radiographic studies of body composition. In *Human Body Composition*, Vol. 6, p. 211. Ed. by G. A. Harrison. Symposia of the Society for the Study of Human Biology. Pergamon, Oxford.
- Tanner, J. M. (1969). Growth and endocrinology of the adolescent. In *Endocrine and Genetic Diseases of Childhood*, p. 19. Ed. by L. I. Gardner. Saunders, Philadelphia and London.
- Tanner, J. M. (1970). Puberty and adolescence. In *Child Life and Health*, 5th ed., p. 188. Ed. by R. G. Mitchell. Churchill, London.
- Tanner, J. M., Prader, A., Habich, H., and Ferguson-Smith, M. A. (1959). Genes on the Y-chromosome influencing rate of maturation in man: skeletal age studies in children with Klinefelter's (XXY) and Turner's (XO) syndromes. *Lancet*, **2**, 141.
- Teller, W. M. (1967). Die Ausscheidung von C₁₉- und C₂₁-Steroiden im Harn unter normalen und pathologischen Bedingungen der Entwicklung und Reifung. *Zeitschrift für die gesamte experimentelle Medizin*, **142**, 222.
- Thomson, J. (1954). Birth weight and weight gain at six months. *Health Bulletin (Edinburgh)*, **12**, 25.
- Van de Wiele, R. L., Bogumil, J., Dyrenfurth, I., Ferin, M., Jewelewicz, R., Warren, M., Rizkallah, T., and Mikhail, G. (1970). Mechanisms regulating the menstrual cycle in women. *Recent Progress in Hormone Research*, **26**, 1.
- Van Wieringen, J. C., Wafelbakker, F., Verbrugge, H. P., and De Haas, J. H. (1968). *Groei-diagrammen 1965 Nederland (Growth Diagrams 1965, Netherlands; with a summary in English)*. Wolters-Noordhoff, Groningen.
- Visser, H. K. A. (1966). The adrenal cortex in childhood. Parts I and II. *Archives of Disease in Childhood*, **41**, 2 and 113.

- Visser, H. K. A., and Degenhart, H. J. (1966). Excretion of six individual 17-ketosteroids and testosterone in four girls with precocious sexual hair (premature adrenarche). *Helvetica Paediatrica Acta*, **21**, 409.
- Werff ten Bosch, J. J. van der (1965). Control of puberty by endocrine and other factors. *Proceedings 2nd International Congress of Endocrinology (London)*, Part 2, p. 833. (Internat. Congr. Series No. 83) Excerpta Medica Foundation, Amsterdam and New York.
- Werff ten Bosch, J. J. van der (1969). Isosexual precocity. In *Endocrine and Genetic Diseases of Childhood*, p. 544. Ed. by L. I. Gardner. Saunders, Philadelphia and London.
- Wieland, R. G., Yen, S. S. C., and Pohlman, C. (1970). Serum testosterone levels and testosterone binding affinity in prepubertal and adolescent males; correlation with gonadotropins. *American Journal of the Medical Sciences*, **259**, 358.
- Winick, M. (1968). Changes in nucleic acid and protein content of the human brain during growth. *Pediatric Research*, **2**, 352.
- Winick, M. (1969). Malnutrition and brain development. *Journal of Pediatrics*, **74**, 667.
- Woods, M. C., and Simpson, M. E. (1961). Pituitary control of the testis of the hypophysectomized rat. *Endocrinology*, **69**, 91.
- Zachmann, M., Krawczynska, H., Trebo, C., and Prader, A. (1971). Funktionsprüfung der Leydig-Zellen bei Kindern und Jugendlichen. *Schweizerische Medizinische Wochenschrift*, **101**, 1101.