The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration

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During the past decade, possible advancement in timing of puberty has been reported in the United States. In addition, early pubertal development and an increased incidence of sexual precocity have been noticed in children, primarily girls, migrating for foreign adoption in several Western European countries. These observations are raising the issues of current differences and secular trends in timing of puberty in relation to ethnic, geographical, and socioeconomic background. None of these factors provide an unequivocal explanation for the earlier onset of puberty seen in the United States. In the formerly deprived migrating children, refeeding and catch-up growth may prime maturation. However, precocious puberty is seen also in some nondeprived migrating children. Attention has been paid to the changing milieu after migration, and recently, the possible role of endocrine-disrupting chemicals from the environment has been considered. These observations urge further study of the onset of puberty as a possible sensitive and early marker of the interactions between environmental conditions and genetic susceptibility that can influence physiological and pathological processes. (*Endocrine Reviews* 24: 668–693, 2003)

I. Introduction

PUBERTY RESULTS FROM the awakening of a complex neuroendocrine machinery in which the primary mechanism is still unclear (1). A peculiarity of sexual maturation in the human species is the 4- to 5-yr physiological variation in age at onset of puberty that is observed among normal individuals despite relatively similar life conditions (2). This variability involves genetic factors, as indicated by the studies on heritability of menarcheal age (3), although the molecular determinants are yet to be identified. Other factors such as ethnicity, nutritional conditions, and secular trends have been shown to influence the physiological range in age at the onset of puberty (4, 5). In these conditions, the age limits used to define sexual precocity are necessarily subject to local assessment and regular revision. Whereas reference data seemed to have stabilized in most industrialized countries during the 1990s, two recent American studies (6, 7), which were reviewed by Lee *et al.* (8), highlighted an unexpected and unexplained advance in physiological age at the onset of breast development. These findings urged us to examine the current variations in timing of puberty around the world and the related age limits for sexual precocity. In addition, new aspects regarding the etiology of sexual precocity provided another reason to consider the differences in timing of puberty worldwide. Most patients with sexual precocity are diagnosed as idiopathic, and no causative process is found at brain imaging (9, 10). Recently, a special form of sexual precocity has been described in foreign children adopted from developing countries to Western Europe. The occurrence of early or precocious sexual maturation in such a unique situation of changing environment was originally described in Indian girls adopted in Sweden (11). Subsequently, similar observations were made in several European countries and involved children from various countries (12–18).

The aim of this review is to address the significance of early

onset of puberty in children living in their home countries or migrating to other countries. Emphasis will be put on the differences in age limits for pubertal development between countries and ethnic groups. The possible etiologies for advancement in timing of puberty in some conditions will be discussed in the light of our current understanding of the mechanism of the onset of puberty.

II. Normal Puberty and Variations in Timing

A. Clinical indicators

Although the concerns about sexual precocity and changes in timing of puberty appear to be much greater in girls than in boys, these issues must be addressed in both sexes, in a comprehensive and comparative perspective. In boys, the first sign of pubertal development is an increase in testicular volume above 3 ml, consistent with Tanner G2 stage (2, 9). This change, however, can be observed only by thorough evaluation at physical examination (2, 19). There is no reliable event that can be recalled to time male pubertal development when taking a medical history. In girls, the earliest manifestation of puberty is acceleration in growth velocity, which, however, is difficult to ascertain because it requires several accurate height measurements each year (20). The commonly used markers of the timing of female puberty are thelarche and menarche, of which different characteristics are summarized in Table 1. Thelarche is the first appearance of breast development defined as Tanner B2 stage (2). This relatively obvious pubertal sign might not be easily distinguished from fat tissue in slightly obese girls. Importantly, the appearance of pubic hair is dependent primarily on testicular androgens in boys and on adrenal androgens in girls. The developmental increase in adrenal androgen secretion is referred to as adrenarche and occurs independently of the pituitary-gonadal maturation or gonadarche (8, 21, 22). Thus, development of pubic hair in girls does not provide any information on pituitary-ovarian maturation. The evaluation of Tanner stages can be obtained by self-assessment or physician's assessment. The self-assessment of pubertal characteristics has been shown to be nonreliable (23), although the answers of adolescents to a global question on development compared with their peers can be a valid approach (24). The assessment of Tanner stages by professionals provides more reliable information than self-assessment but involves significant variations between observers (23). The Tanner stages

provide semiquantitative information with less accuracy than using the menarcheal age to assess the timing of pubertal development.

Menarche, the occurrence of first menstruation, is a unique and relatively late marker of female puberty (2). The menarcheal age can be assessed directly and preferably by the status quo method, which consists of asking girls in different age groups whether or not they have had the first menses. Retrospective assessment through the recall method leads to comparable data in some conditions (25), although a longer recall period (26) and socioeconomic or cultural biases (27) can result in a loss of accuracy. The menarcheal age is highly significantly correlated with age at the appearance of breast buds (2) and is therefore considered to be an indicator of the onset of puberty. Menarche, however, might provide information different from breast budding because the former is the endpoint of a complex sequence of maturational events, whereas the latter results more simply from onset of estrogenic action. In addition, there are possible confounding factors that can explain that the ages at the onset of breast development and at menarche are not strictly correlated (28). Among these factors, a decrease in duration of puberty or time period between B2 stage and menarche has been observed in subjects with late onset of puberty when compared with early onset of puberty (28–30). Also, any factor stimulating breast development independently of hypothalamic-pituitary-ovarian maturation can account for dissociation between the ages at breast budding and at menarche. In fact, these two events might show different responses with different sensitivity to the biasing effects of exogenous substances.

In the published literature on the timing of puberty, the data are given either as mean ± SD in some studies, assuming that the data are normally distributed, or as median and centiles in other studies. This issue is important because the mean and median are comparable only when the distribution of data is Gaussian (Fig. 1A). This can be the case in a well-off setting, as indicated by the symmetrical distribution of centiles of menarcheal age in North American girls (31). By contrast, an asymmetrical distribution of data with increased variability toward late ages (Fig. 1B) can be observed in an underprivileged setting (32). In these conditions, the calculated mean age will be greater than the median. An increased prevalence of early sexual maturation in a population such as migrating children can result from either a subset of fast maturers causing an asymmetrical distribution of ages at

TABLE 1. Differences between thelarche and menarche used as markers of the onset of puberty

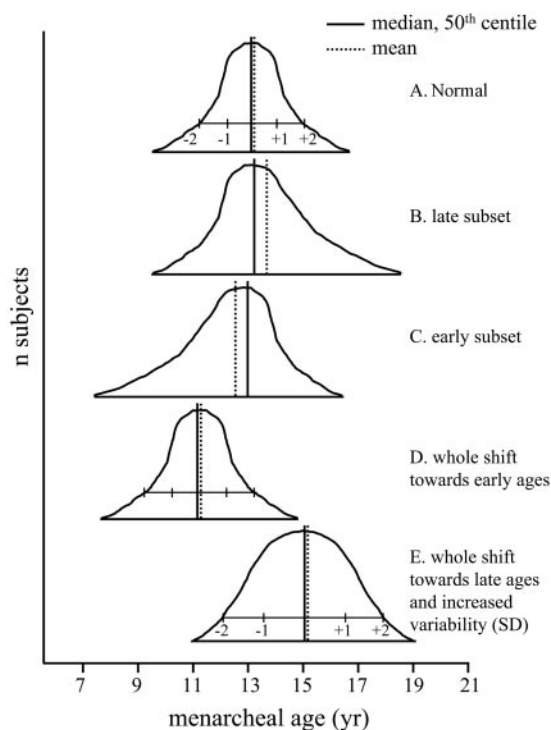|	Thelarche	Menarche
Assessment by a professional	Direct (physical exam)	Indirect (history)
Self-assessment	Possible	Required
Method of assessment	Inspection (and palpation)	Recall or status quo
Reference	Tanner stage picture and description	–
Accuracy	Limited (staging)	Dependent on precision of information
Reliability	Observer dependent (confounding adipose tissue. . .)	Interviewer dependent (questions) and subject-dependent (memory)
Relation to the sequence of pubertal events	Close to onset, tempo independent	Distant from onset, tempo dependent
Relation to hypothalamic-pituitary-ovarian axis	Thelarche possibly involving gonadotropin-dependent ovarian secretion or exogenous estrogens	Likely involving the whole axis

FIG. 1. Schematic representation of the distribution of timing of puberty (*e.g.*, menarcheal age) in different conditions. The important parameters are the median and mean ages, the symmetry or asymmetry of distribution, and the variability as expressed by the SD values (−2 SD to +2 SD illustrated).

onset of puberty (Fig. 1C) or a shift of the whole population toward earlier timing of puberty (Fig. 1D), or both. The magnitude of the SD provides an index of variability in timing of puberty. For instance, during the 19th century (33), not only was the average menarcheal age later but also the SD was greater than today (Fig. 1E).

Because food and/or energy availability influence sexual maturation (4, 34) and are unequally distributed around the world, the age limits for puberty are to be discussed separately in well-off and underprivileged conditions. Such a distinction provides a basis to assess differences in timing of onset of puberty in children moving from developing countries to Western Europe. Also, the observations in the United States and in Western Europe will be separated for the purpose of comparison between two industrialized settings.

B. Age references in well-off conditions

In the United States, Mac Mahon (35) reported a mean menarcheal age of 12.8 yr in 1973. Very similar data (12.7 yr) were reported by Tanner and Davies (31) in 1985 with a median age of 10.9 yr for onset of breast development. This is very close to the data obtained in most European countries (Fig. 2). In 1997, however, a publication from the American Academy of Pediatrics-Pediatric Research in Office Settings (PROS) network reporting on more than 17,000 girls led to an adjustment in the above-mentioned limits in the United States (6). These authors found the mean age at B2 to be 10.0 yr in White American girls and 8.9 yr in African-American girls, with −2 SD limits of 6.3 and 5.0 yr, respectively. These

findings generated comments on the possible overestimation of breast development because assessment was made through visual inspection only, whereas palpation may be required to distinguish between adipose and glandular tissue (8, 36). In addition, the data were not corrected for the difference in racial representation that resulted from only 10% of the participants in the PROS study being African-Americans (37). This, together with other possible biases such as the increased variance due to the involvement of multiple observers, raises the issue of whether or not the onset of puberty is shifted toward earlier ages in the United States (36, 37). In another large cross-sectional American study (the National Health and Nutrition Examination Survey, NHANES III), a similarly early median age of 9.7 yr at B2 was found in White Americans (7), although slightly less advanced median ages of 10.4 yr (White Americans) and 9.5 yr (Black Americans) were recently reported in subgroups from that cohort (38). The large NHANES III study, however, was not different from the PROS study in that it was cross-sectional and involved many different observers, without mention of the possible or systematic use of palpation to assess breast tissue development. Therefore, confirmation of those findings may warrant a carefully designed prospective longitudinal study involving a limited number of observers who use breast palpation to assess development. Interestingly, the mean menarcheal age found in the PROS study (6) did not show the same shift as age at the onset of breast development because age at menarche (12.9 yr in White Americans and 12.7 yr in Black Americans) was unchanged when compared with the data reported earlier (31, 35). Here also, a bias was possible in the PROS study where the subjects were aged 12 yr or less and mean menarcheal age was extrapolated by probit analysis. However, in the NHANES III study (7), which involved subjects aged up to 17 yr, menarche occurred in White Americans at an age (12.5 yr) similar to that extrapolated in the PROS study. The similar menarcheal ages observed in the United States recently (6, 7) and several decades earlier (31, 35) suggest that the secular trend toward earlier menarche has stopped. This issue was more specifically addressed in two recent studies based on the NHANES III data and the National Health Examination Survey (NHES) data (39, 40). In these two studies, the median menarcheal age in the U.S. girls studied around 1990 was 12.43 or 12.54 yr with a reduction of 0.34 yr in 30 yr or 0.21 yr in 25 yr, respectively. These differences are much less than that described for breast development in the same period. Is it possible that the secular trend toward earlier menarche has been underestimated in the two large cross-sectional American studies (6, 7)? Such a possibility might be consistent with the data from the Bogalusa Heart study, which reported on a smaller biracial cohort of 1082 girls studied in 1992–1994 (41). In this study, the mean menarcheal age was found to be 11.4 and 11.5 yr in African-American and White-American girls, respectively, which is much earlier than in the PROS and NHANES studies and indicates an important secular trend, because in 1978–1979, the menarcheal age was 12.3 and 12.2 yr, respectively, in the same area (41). Several factors might account for this discrepant observation. First, local environmental changes in the semirural area of Bogalusa may be greater than in the United States in general, resulting
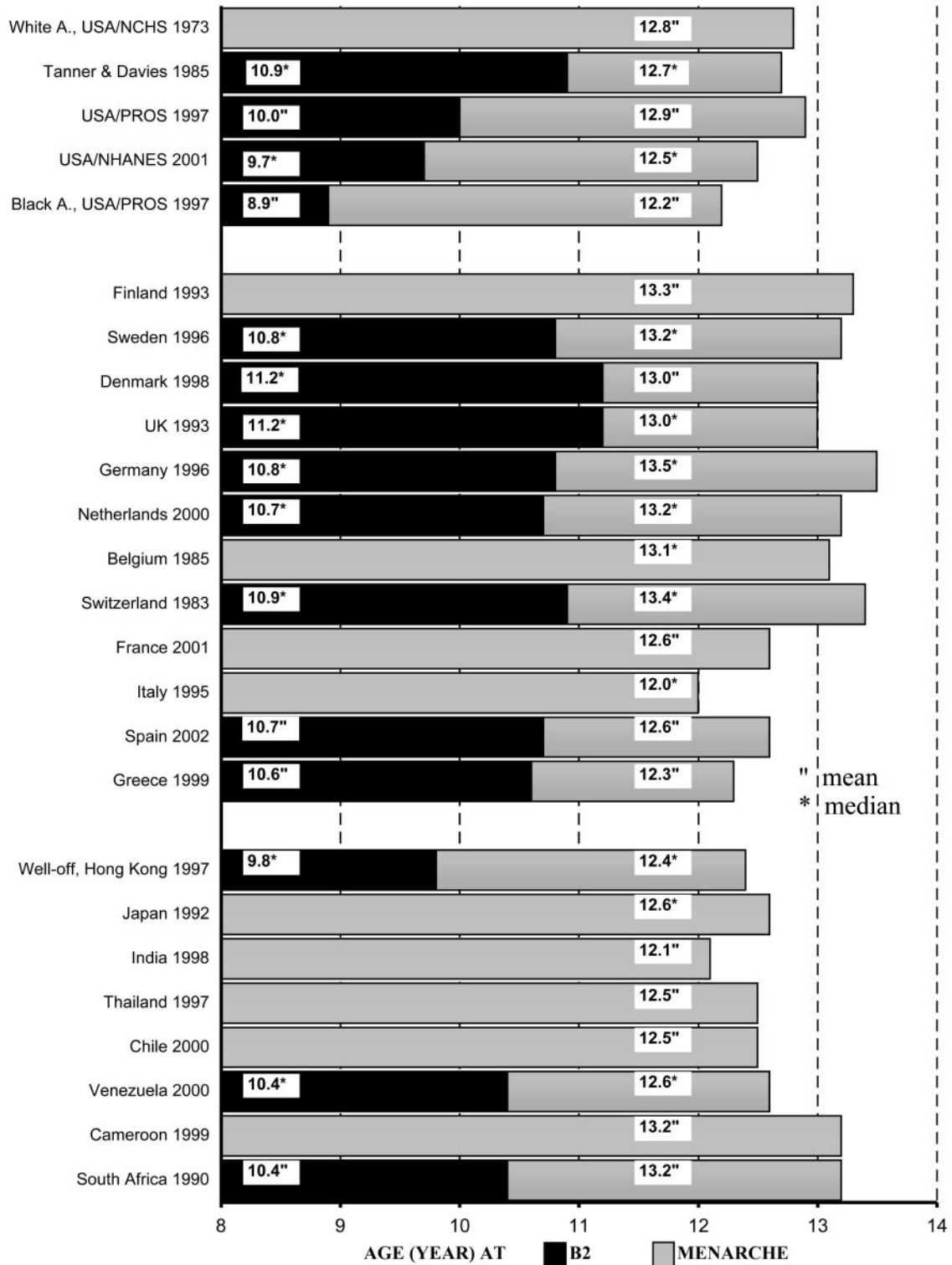
FIG. 2. Average (mean or median) ages at onset of breast development (B2) or menarche in different well-off populations around the world. The most recently published data were used to provide an update.

in faster increase in body fatness. Between 1974 and 1994, the prevalence of body mass index (BMI) greater than the 85th percentile among 5- to 14-yr-old subjects has increased by 22% (from 15 to 37%) in the Bogalusa study (42). This race- and gender-independent increase is much more than the 7%

increase found using the same criteria in the NHES study between 1963 and 1991 in 6- to 17-yr-old subjects (43) and the 8% increase found in the adult U.S. population (44). Another bias in the report from the Bogalusa cohort (42) was that two different cohorts of subjects were studied at a 15-yr interval.

The impact of such a biasing factor is likely because a recent analysis including a longitudinal subset of 2058 subjects showed that the median menarcheal age in the Bogalusa cohort was 12.6 yr in White Americans and 12.3 yr in Black Americans, with a secular reduction of 0.8 and 0.17 yr during the past 20 yr, respectively (45). In a recent longitudinal study of an equal proportion of White and Black Californian girls, similar mean menarcheal ages of 12.7 and 12.0 yr, respectively, were reported (46). In a cross-sectional study performed in the 1970s and involving 84% of White American girls, the mean menarcheal age was 12.2 yr (47). Thus, it is likely that the average menarcheal age has almost stabilized in the United States, whereas age at onset of breast development may have declined. As already mentioned, the increasing difference between trends in ages at B2 and menarche might involve an inverse correlation between age at onset of puberty and duration of puberty (28–30). However, a trend toward increasing time length between B2 and menarche is somewhat contradictory to the observation of a secular acceleration of the progression or tempo of pubertal development in Dutch and Swedish boys and girls (48). Alternatively, unidentified external factors might cause breast development to start earlier without affecting menarcheal age.

Data published during the last 20 yr on the age at onset of breast development and menarche in different European countries are represented in Fig. 2 following a north-south gradient (49–64). The average menarcheal age in Western Europe currently varies between 12.0 yr in Italy (61) and 13.5 yr in the eastern part of Germany (55). The mean menarcheal ages in France and the Mediterranean countries (60–64) are lower than in other Western European countries (49–59). As reviewed by Eveleth and Tanner (65), this points to a geographical difference that can involve genetic or ethnic factors as well as environmental factors. Although data on age at the onset of breast development are available only in some of these European countries, they do not indicate any obvious geographical gradient (Fig. 2). In some Asian, African, and South-American countries, girls living in privileged conditions also show differences in average menarcheal age as compared with those living in underprivileged conditions. Well-off Chinese (66), Japanese (67), and Indian (68) girls have menarcheal ages similar to girls from the Mediterranean countries. The age at B2, however, is 0.8 yr earlier in Hong Kong (66) than in Greece (64), suggesting a difference in tempo of pubertal development or the involvement of factors affecting separately the age at B2 and the menarcheal age. In Thailand (69) and South-American countries such as Chile (70) and Venezuela (71), the menarcheal age averages 12.5 yr. In Cameroon (72) and South Africa (73), menarche occurs in well-off black girls at a mean age of 13.2, which is about 1 yr later than in African-American girls (6, 46, 47).

In the pioneering work of Marshall and Tanner (19), which provided age references for male pubertal development in 1970, the mean age for G2 stage was found to be 11.6 yr in the United Kingdom. Very similar data have been reported for the United States (11.5 yr) in 1985, Sweden (11.6 yr) in 1996, The Netherlands (11.5 yr) in 2001, and Switzerland (11.2 yr) in 1983 (31, 51, 57, 74). In a longitudinal Spanish study, the mean age at G2 was 12.3 yr (63). These stabilized references are in contrast to the lowered median age of 9.7 yr at G2 that has been reported from the American NHANES III study, which was performed in the period 1988–1994 (75). This study involved 25% of White Americans, 37% of Mexican Americans and 38% of African Americans with respective median ages at G2 of 10.1, 10.4, and 9.5 yr, a difference that was not significant (72). In a more recent subgroup study from the same cohort, similar ages were reported (38). Those data were obtained based on visual inspection without palpation of testicular volume or assessment of testicular size. As mentioned in an editorial comment by Reiter and Lee (76), that bias may be important because the increase in testicular volume or size is critical in the evaluation of the G2 stage of Tanner. The inaccuracy of visual assessment might also account for the one-stage variance between physicians involved in the study (76) and the surprisingly long time interval of 2 yr between G2 and P2 stages (75), whereas this interval was found to be 1 yr by others (51, 59). There are unfortunately no data available from comparable studies. In the NHES study, G2 data were not available (77). In a longitudinal study of 78 boys, Roche *et al.* (78) reported a mean age of 11.3 yr at G2, but the validity of these data may be limited because of self-assessment. Biro *et al.* (79) also performed a longitudinal study, but they used modified global stages of puberty that are not comparable. Thus, it is difficult to draw conclusions before we have additional data from a prospective study with assessment of testicular volume or size. The stable mean age at G5 (15.3 yr) in the NHANES III study is in contrast with the earlier age at G2. This would suggest that the tempo of male puberty is, in fact, decreasing. In some countries such as Hong Kong where the median ages at G2 and B2 are 11.4 and 9.8 yr, respectively (66, 80), the age at G2 in boys has not changed, whereas the age at B2 is declining. Although girls classically precede boys by an average of 0.8 yr for the onset of puberty (51, 53, 57), such a sexual dimorphism has not been found any longer in two recent American and German studies where identical ages at B2 and G2 were reported (6, 55, 75, 81). Such discrepancies point to the need to compare studies conducted using similar design and methods in different countries.

C. Age references in underprivileged conditions

In developing countries, inequalities related to socio-economic status or life setting (urban *vs.* rural) are still prominent and might account for important variations in timing of puberty within and among countries (5, 65). Secular trends can still be observed in developing countries because of current changes in living standards. When subgroups of girls in well-off and underprivileged conditions are compared in some countries (Fig. 3), the impact of these differences in living standards is obvious (5, 68, 72, 73, 82, 83). The socioeconomic status of the study group is not always specified, and we can then assume an average living standard. In recent reports from Nigeria, Guatemala, or Colombia (32, 84, 85), later ages at menarche were observed compared with well-off girls from the neighboring countries of Chile and Venezuela (70, 71). In countries such as China and Senegal where girls living in
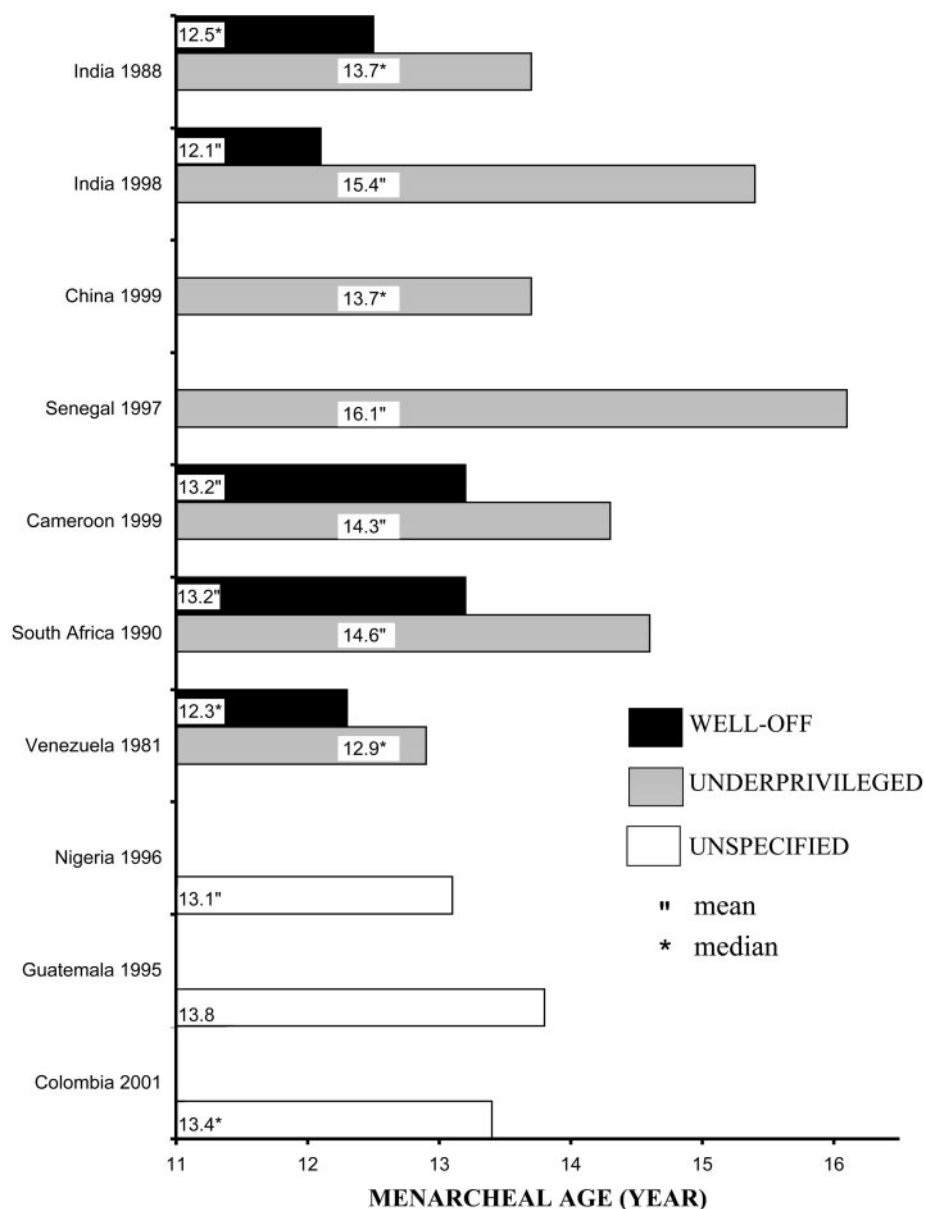
FIG. 3. Average (mean or median) menarcheal age in different developing countries. The data are shown separately for different living conditions.

underprivileged conditions have been studied, the mean menarcheal age is as great as 16.1 yr (86, 87). The variability in menarcheal age can be translated into the coefficient of variation (CV), which is the SD expressed as a percentage of the mean. The CV is greater in underprivileged girls from Cameroon (11.6%) than in privileged girls from the same country (8.2%) (72), although such a difference is not observed in South Africa (73). A low CV (9.2–10.0%) is obtained in other well-off conditions (6, 64, 69). Taken together, these data highlight the crucial role of socioeconomic and nutritional conditions in the timing of puberty. A similar conclusion was drawn in a recent study reviewing menarcheal age in 67 countries (88). These authors pointed out that, on a large scale, extrinsic factors were crucial: the effects of early involvement in physical activities on energy expenditure were emphasized in relation to frequent illiteracy rate.

D. Secular trends

Between the mid-19th and the mid-20th century, the average menarcheal age decreased remarkably from 17 to under 14 yr in United States and in some countries in Western Europe (4, 5, 9, 65, 89, 90). This was a steady process because the average menarcheal age decreased uniformly until the 1960s. This decline, however, varied among countries (Fig. 4). A decline of about 0.3 yr per decade could be calculated from the Norwegian and Finnish data (5, 65, 90) and the prospective American studies (89, 90). In France, the slope of the linear regression calculated for the mean menarcheal age between 1841 and 1974 accounts for a decline of 0.175 yr per decade (33). Such a difference in time shift can be related to the fact that, by the mid-19th century, menarcheal age in France (~15 yr) was already earlier than in Scandinavia (~17 yr) (5, 33, 65). This suggests that the north-south Euro-
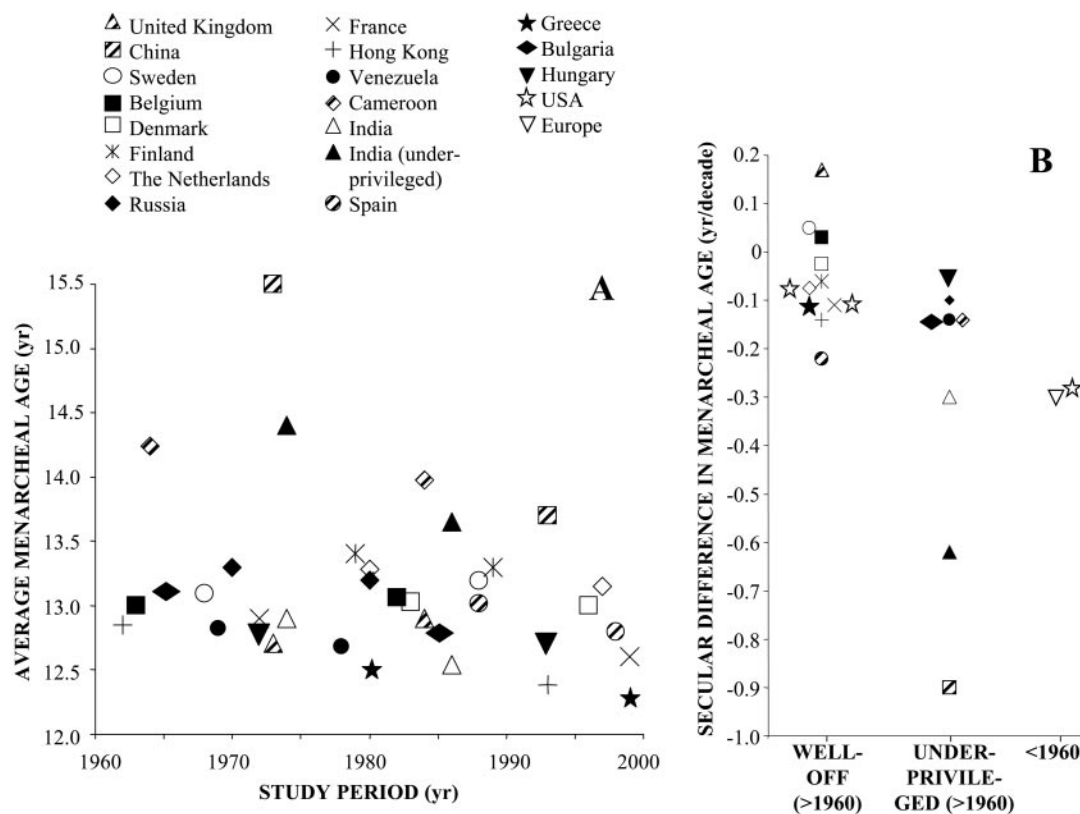
FIG. 4. Secular trend in menarcheal age in different countries around the world. A, Twin set of average data obtained after 1960 in different countries at several 10-yr intervals. B, Secular difference in menarcheal age calculated from those data. For the purpose of comparison, the average secular trend observed before 1960 in the United States and in Europe is also shown.

pean gradient in menarcheal age has existed for more than a century and was greater in the past than today.

The studies performed after 1960 provide less uniform data as indicated by the recently reported changes in average menarcheal age, which are quite different among countries (Fig. 4). In the United Kingdom, Sweden, and Belgium, a modest increase in menarcheal age is seen (+0.14, +0.05 and +0.03 yr per decade, respectively), which provides some evidence that the secular trend toward earlier menarche has come at least to an arrest (50, 58, 91). In Denmark, Finland, The Netherlands, Russia, France, and Greece, the trend is still negative but very moderate and much less rapid than formerly because the decline does not exceed −0.12 yr per decade (48, 49, 52, 56, 64, 92, 93). This figure is similar to that reported recently in the United States based on NHANES/ NHES data (39, 40). A relatively slow decline of −0.14 yr per decade is now observed in countries such as Hong Kong, Venezuela, and Cameroon, which developed more recently than the United States and Western European countries (66, 72). In Spain, it seems that the secular trend is still quite marked with a decline of −0.22 yr per decade during the 1990s (94). In India and China, the most recent reports indicate that the secular trend in reduction of menarcheal age is still obvious, with a decline either comparable to the former figure in the United States and Western Europe or twice as fast (83, 86). A similar finding has been made in some countries from Eastern Europe, such as Bulgaria, where the trend is still continuing (95). This set of updated information from

all around the world is in concordance with the evolution of living standards in different countries and further supports the role of nutritional and health status or socioeconomic conditions. Recently, Anderson *et al.* (40) reported that the secular trends toward earlier menarche and more elevated body weight for height in the United States could be associated because increased BMI was predictive of the increased likelihood of being menarcheal after adjustment for age and race. As reported recently from the Bogalusa Heart Study, a more obvious secular trend in African-American girls compared with white Americans indicates the possible combination of environmental and ethnic factors (45). In Denmark, Olesen *et al.* (96) reported that the negative trend seemed to have resumed after a halt period. Olesen *et al.* emphasized that, even in this industrialized country, the menarcheal age can still be delayed in some subgroups, thus accounting for the remaining potential of an active secular trend (96). Then, the differences between urban and rural or well-off and poor living conditions that have been extensively documented in developing countries (5, 65) might still be relevant to the so-called developed countries. Variations in particular subgroups may not be apparent from whole population data. Mau *et al.* (97) reported recently that in Denmark, menarcheal age had not changed between 1964 (13.3 yr) and 1990–1991 (13.4 yr).

The variability in menarcheal age in France as reflected by the CV was greater in the mid-19th century (17.3%) than in the mid-20th century (10.0%) (33, 60). It appears, however,

that between the 1930s and the 1960s in the United States, CV was 9–10% and did not change any longer, whereas the decline in average menarcheal age was still progressing (89). In China, where the secular trend in decline of menarcheal age was still important between the early 1970s and the early 1990s (Fig. 4), there was only a modest concomitant reduction in that CV from 11.9 to 9.8% (87). Such a dissociation between the mild changes in variability of age at menarche and the steady decline in average menarcheal age suggests that both parameters are influenced by different factors or differently by the same factors.

Some authors have looked into the secular trend dynamics using other markers such as the onset of breast development in girls and genital development in boys. In Sweden and the United Kingdom, the onset of breast development has been found to be slightly earlier in 1980 than in the 1960s or 1970s (48). In Denmark (97), the average age at onset of breast development even tended to increase between 1964 (10.6 yr) and 1990–1991 (11.2 yr). In Europe, there is no evidence of marked secular reduction in average age at B2 such as shown in the United States (6, 7). The age at G2 has shown some increase in The Netherlands during the last decades, whereas a decrease has been observed in Sweden (48). Although a methodological bias is possible due to the small number of boys in the G2 stage, such discrepant observations might point to some country-specific environmental changes. These observations are also raising important issues regarding the significance of the data in relation to the markers used to evaluate the timing of pubertal development as discussed above.

## III. Precocious Puberty

A. Age limits

On the basis of the above mentioned average ages at onset of pubertal development and assuming a Gaussian distribution in the normal population, abnormally precocious sexual development has been defined in Europe as less than 8 yr for the B2 stage in girls and less than 9 yr for the G2 stage in boys (10, 98, 99). These age limits, which are above the 99th centile, have been used for several decades and are still used currently. Similar age limits were thought to be relevant to the United States until the publication of the PROS study (6) prompted Kaplowitz and Oberfield (100) to recommend, on behalf of the Lawson Wilkins Pediatric Endocrine Society, to reset the age limit for nonphysiological onset of breast development at 7 yr in Caucasian girls and 6 in African-Americans. Some American colleagues, however, did not share the opinion of Kaplowitz and Oberfield and advocated a possible recruitment bias through pediatricians' offices (36). In addition, the unexplained dissociation between earlier breast development and relatively unchanged menarcheal age was raising indirectly the issue of the reality of breast development estimated through visual inspection. The definition of appropriate age limits is crucial to restrict diagnostic evaluation and possible therapeutic intervention to children with abnormal precocious development (98, 99). In a recent review of 223 patients referred for sexual precocity occurring between 7 and 8 yr in white girls or 6 and 8 yr in black girls,

Midyett *et al.* (101) found that 47% showed both breast and pubic hair development, 35% had bone age at more than 3 SD above chronological age, and 12% appeared to have a non-idiopathic form of sexual precocity. The authors concluded that occurrence of sex characteristics between 6 and 8 yr is not necessarily benign and may warrant diagnostic and therapeutic intervention (101). Thus, the question of age limit for sexual precocity does not have any definitive and unequivocal answer.

B. Common etiologies

Sexual precocity is classified as central, gonadotropin-dependent, *i.e.*, driven by the central nervous system, when it results primarily from early hypothalamic-pituitary maturation (8, 99). Central precocious puberty represents four fifths of the total number of patients with precocious puberty (99, 102) and is much more frequently seen in girls than in boys. Idiopathic central precocious puberty is diagnosed when early pubertal development (including acceleration of growth and bone maturation) is associated with a pubertal pattern of gonadotropin secretion (increased LH secretion) and when there is no evidence of organic cause provided through history, physical examination, or brain imaging (9, 98). Among patients with central precocious puberty, the proportion of idiopathic forms varies between 58 and 96%, as reviewed recently (103, 104). This proportion is greater in girls than in boys, who show a higher prevalence of recognizable organic forms. As shown in Fig. 5, the female to male ratio found among the patients with central precocious puberty in the studies published between 1961 and 1990 was relatively similar, around 3:1 to 4:1 (102, 105–112). In the same studies, the idiopathic to organic ratio was around 2:1, indicating that two thirds of the patients had idiopathic forms and one third had organic forms with identified neurogenic etiologies. In more recently published studies from four European countries as well as from the United States (10, 17, 18, 113–115), the proportion of female patients and idiopathic forms has clearly increased (Fig. 5). In a recently published American series, however, the sex ratio and etiological distribution were similar to the data from early studies despite the changing age limits for sexual precocity in the United States (116). It should be noted that this study reported on final height and involved patients diagnosed several years earlier and referred to the NIH with possible recruitment biases. The changing gender and etiological distribution of patients with precocious puberty in the United States could have resulted from the recently observed reduction in age at onset of puberty, before the age limits for sexual precocity were revised. Such an explanation, however, is unlikely in Europe where the physiological age at onset of puberty and the age limits for sexual precocity did not change during the past decade. An increased variability in timing of puberty without change in the mean ages could account for an increasing number of girls with idiopathic forms. Based on the diagnostic advances made during the past decades using nuclear magnetic resonance imaging, an increasing proportion of idiopathic forms would not have been expected. Another clue to the changing epidemiology of central precocious puberty could be the occurrence of new etiologies as

FIG. 5. Gender and etiological distribution of patients with central precocious puberty in the series published between 1961 and 2001 in relation to the year of publication and the country of study (DK, Denmark; F, France; UK, United Kingdom; NL, the Netherlands; B, Belgium). The number of patients and reference (in *parentheses*) are indicated at the *top of each bar*.
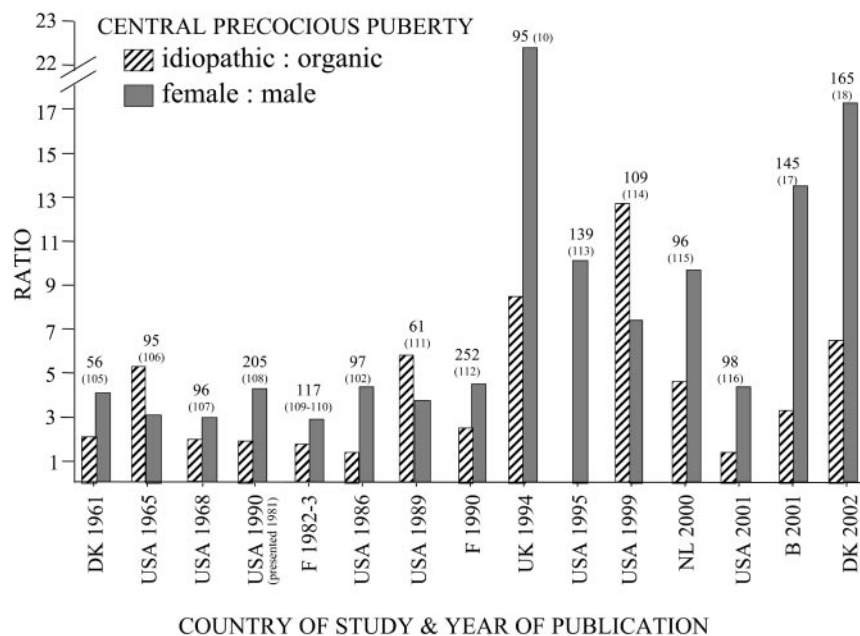
suggested by the increasing proportion of migrating children who develop sexual precocity, as discussed below.

In peripheral, gonadotropin-independent sexual precocity, the primary event is increased secretion of adrenal or gonadal sex steroids or exposure to exogenous steroids (10, 102). Peripheral sexual precocity represents one third to one fifth of the total number of patients with precocious puberty (10, 117) and involves both sexes. Some forms of peripheral sexual precocity predominate in boys, such as chorionic gonadotropin-secreting tumors and familial gonadotropin-independent precocious puberty or testotoxicosis, which is caused by activating mutations of the LH receptor or constitutive Gsα activity in Leydig cells (10, 117). The latter mechanism also accounts for the McCune Albright syndrome. This form of sexual precocity predominates in girls as well as ovarian cysts and exposure to environmental estrogens (10, 117). Some peripheral or partial forms of sexual precocity, such as isolated premature thelarche, can secondarily evolve into central precocious puberty (98, 103, 117).

C. Children migrating from developing countries

After an initial report from Sweden in 1981 (118), sexual precocity has been reported in children migrating from developing countries to different European countries, primarily through international adoption (11–18). So far, there is only one similar report from the United States published in abstract form (119). Some data from the published series are summarized in Table 2, and methodological aspects are listed in Table 3. In the original Swedish report and the subsequent Dutch, French, and American reports, cohorts of foreign adopted patients were studied, and the mean menarcheal age was evaluated through questionnaires sent out to the families (11, 13, 16, 119). In these studies, the absolute frequency of sexual precocity was undoubtedly increased (Table 3) but was variable among the studies between 13% (11) and 30% (119). In the Swedish cohort study, the men-

archeal ages, although advanced, followed a relatively symmetrical pattern of distribution (11), such as expected in normal adolescents (120). This indicates that advanced puberty was a general feature of the whole cohort (Fig. 1D) instead of precocity being a feature of a particular subset (Fig. 1C). It is of note that the variability in menarcheal age (CV, 11.5–24.7%) in these cohorts (13, 16, 119) can be greater than in the nonmigrating girls living in well-off conditions. Several biases may have influenced the calculation of the frequency of sexual precocity. In the cohort studies, sexual precocity was defined as early menarche, which was reported in the questionnaire (11, 13, 16). Such a definition was different from the patient studies in which early breast development was the first criterion used to define precocity (14, 16–18). This distinction is important because thelarche and menarche may have a different significance (Table 1). India was the only country of origin in the Swedish study (11), whereas several different countries were involved in the other studies (13, 16, 119). The differences in country of origin were unlikely to bias the findings because, in three cohort studies, the average menarcheal age was advanced in comparison with data from the foster country and the country of origin as well (11, 13, 16). In the study by Oostdijk *et al.* (13), mean ages at menarche differed significantly, with the lowest observed in girls from India (11.2 yr) and the highest in girls adopted from South Korea (12.4 yr). In the Swedish study, birth date was uncertain in 28% of subjects, but similar data were obtained when the subsets with certain and uncertain birth date were compared (11). In a study on children adopted from China, 11% were thought to have an inaccurate birth date (121). Birth date uncertainty is a potential bias in all the studies, with possible differences among the countries of origin. This, however, is unlikely to account for false diagnosis of sexual precocity in most migrating children, although such a possibility should be kept in mind for individual patients. More important, the bias of parental concern about early sexual development of their adopted child

TABLE 2. Data from studies on pubertal development in migrating children

Country of study	Yr	A/NA	Subjects (n, gender)	Type of study	Country of origin	Mean age at immigration (yr)	Mean age at B2 (yr)	Mean age at menarche (yr)	Adult height (cm)	Ref.
Sweden	1991	A	107G	Cohort (Q)	1 (India)	3.7	–	11.5[a] (<10 yr, n = 14)	155.0 (n = 66)	11
Belgium	1992	A	8G	Patient (H, E)	–	–	–	–	–	12
The Netherlands	1996	A	446G	Cohort (Q)	4 (Colombia, India, Korea, Indonesia)	2.9	–	12.0	157.7 (n = 310)	13
Italy	1998	A	19G	Patient (H, E)	>1 (India:15/19)	4.4	6.9	–	152.6 (pred.)	14
France	2000	A	10G, 3B	Patient (H, E)	5 (Colombia, Mexico, Brazil, Rwanda, Madagascar)	5.1	7.1	–	–	16
United States	2000	A	52G, 47B	Cohort (Q)	15 (4 continents)	5.4	–	11.3 (n = 30)	–	16
Belgium	2001	A	146B, 193G	Q	51% Russia	3.7	30% early	10.5	–	119
Belgium	2001	A	28G, 1B	Patient (H, E)	17 (4 continents)	3.9	all <8	–	153.1 (n = 7)	17
		NA	12G	Patient (H, E)	15 (4 continents)	3.3	all <8	–	–	17
Denmark	2002	A	23G	Patient (H)	5 (India, Colombia, Sri Lanka, Korea, Vietnam)	2.8	7.5	–	–	18
		NA	10G	Patient (H)	9 (5 continents)	5.7	6.6	–	–	18

A, Adopted; NA, nonadopted; G, girls; B, boys; Q, questionnaire; H, history; E, physical examination; pred, predicted.
[a] Median.

TABLE 3. Methodological aspects in studies on pubertal development in foreign adopted children

Country of study	Yr	Method	Study population (n)	Responders (%)	Absolute frequency of P.P.	Relative risk of P.P.	Biases	Ref.
Sweden	1991	Questionnaire	Adopted children (129)	83	13% of adopted children	–	Precocity based on menarche; single country of origin (India); birth date uncertainty	11
The Netherlands	1996	Questionnaire	Adopted children (1363)	63	–	–		13
France	2000	Questionnaire	Adopted children (250)	40	27% of adopted children	–	Responders more concerned than nonresponders due to increased prevalence of precocity?	16
United States	2000	Questionnaire	Adopted children (339)	–	30% of adopted children	–	Unknown definition of early puberty	119
Italy	1998	Interview/phys. exam	Referred for P.P. (19)	–	–	–	Precocity based on breast development	14
France	2000	Interview/phys. exam	Referred for P.P. (13)	–	–	–	Untreated not included; incomplete adoption registry; nonreferral or referral to other specialists	16
Belgium	2001	Interview/phys. exam	Treated for P.P. (29)	–	26% of idiopathic central P.P.	×80		17
Denmark	2002	Interview/phys. exam	Referred for P.P. (23)	–	16.1% of idiopathic central P.P.	×20	Selection bias?	18

P.P., Precocious puberty; phys. exam, physical examination.

may have influenced the decision to respond to the questionnaire, accounting for overrepresentation of early maturers in the responding families.

In addition to the cohort studies of foreign adopted children, additional evidence of early timing of puberty has been provided by the observation of sexual precocity in individual foreign adopted patients described as an entity in Italy (14) and France (16) or in comparison with the whole group of patients seen or treated for central precocious puberty in Copenhagen (18) and in Belgium (17). In Belgium, foreign migrating children represented 28% of the patients seen with central precocious puberty, including the organic forms (17). The foreign adopted children represented 26% of the patients with idiopathic central precocious puberty (Table 3). These data were used to calculate the relative risk of sexual precocity in foreign adopted patients in comparison with children native to Belgium (17). In native Belgian children, the incidence of sexual precocity based on the patients treated in the seven university departments in the country was found to be 0.01% of the entire population of children. This figure was consistent with the overall incidence of 0.01–0.05% estimated by Gonzalez (122). Using the database from the national adoption registries, an 0.8% incidence of precocious puberty in adopted children was calculated, accounting for an 80-fold increased risk of sexual precocity in comparison with Belgian natives (17). In similar conditions, the study in Copenhagen showed that foreign adopted children accounted for 16% of the patients referred for and diagnosed with sexual precocity (18). Using the database from the Danish immigration office, a 20-fold increased risk was calculated in comparison with Danish natives (18). How can the discrepancy between these data and those from the cohort studies be explained? The factors contributing to possible overestimation in the cohort studies have been discussed earlier. In addition, some factors may have caused underestimation in the patient study. Some patients may have been referred, but at such a final stage of development that treatment was not justified. Patients may also have not been referred, because early development was thought to be a normal characteristic of foreign children (123). In this respect, it is of note that Mason and Narad (123), referring to their survey of children adopted in the United States from Eastern Europe (119), mentioned that such girls with a mean (±SD) age at B2 of 8.8 ± 2.5 yr would be nearly normal and not meet the criteria for early puberty. This statement could be understandable in the current context of early thelarche in the United States (6, 7) and might explain why sexual precocity is rarely reported from the United States where more than 100,000 foreign children were adopted in the decade 1990–2000 (123). These adopted girls, however, showed much earlier menarche (10.5 ± 2.6 yr) than American girls. In the European studies, one could argue that nonreferral would apply to Belgian or Danish native children as well as to adopted children. Also, the obviously incomplete adoption registry database in Belgium, due to foreign adoption through organizations not appointed by the state, could account for overestimation of the incidence of sexual precocity. Finally, it is possible that the more careful medical attention paid to the foreign adopted children contributes to overestimation of sexual precocity in comparison to children that are born in the foster country (124).

In the foreign children with sexual precocity, evidence of early hypothalamic-pituitary maturation and normal brain imaging has been provided, leading to the diagnosis of idiopathic central precocious puberty (14, 16, 17). In all the studies, sexual precocity was seen much more frequently in foreign girls than in boys (11–14, 16, 17, 119). Such a sexual dimorphism might reflect the general and unexplained female preponderance of idiopathic central precocious puberty. However, a precise cause influencing specifically the female endocrine system cannot yet be excluded. The early hypotheses to explain sexual precocity in foreign adopted children after migration have incriminated the transition from an underprivileged to a privileged environment (11, 12). A new perspective has come from the recent Belgian report indicating that 12 patients from a total group of 145 were foreign children moving together with their original families without past history of deprivation (17). The observation of both nonadopted and adopted foreign children among the patients with precocious puberty was also found in Denmark (Table 2). The occurrence of precocious puberty in nonadopted migrating children suggests the possible role of factors related to migration and change of environment. Although the impact of former nutritional and emotional stress is less likely in children moving together with their original families, it is possible as well that such children are relieved from some stressful conditions after leaving their country.

The available data on actual or predicted adult height in migrating girls, including those with early or advanced puberty (11, 13, 14, 17), indicate that the average final height was close to or below the third centile of national references in the foster countries (Table 2). The interpretation of height data is difficult because of the possible role of ethnic differences, unknown short parental height, and intrauterine growth retardation (IUGR) in addition to precocious puberty. The observation of short adult stature prompted several clinicians to study the effects of combined GnRH agonist suppression of puberty and stimulation of growth with GH (125, 126). Pubertal growth and final height are obviously very important factors in relation to changes in pubertal timing and secular trends in the general population as well as in migrating children. These aspects, however, involve many factors beyond the control of pubertal timing and will not be discussed in the present paper.

IV. Possible Mechanisms of Variations in Timing of Puberty around the World and after Migration

Puberty and reproduction are determined by changes in the secretion of the pituitary gonadotropins, LH and FSH, which are dependent on the frequency and amplitude of pulsatile GnRH neurosecretion from the hypothalamus (1, 9). The timing of puberty can be influenced by signals involving neurotransmitters and neuropeptides that originate in the hypothalamus, in addition to peripheral or gonadal signals. Signals linked to the environment such as nutrition, light, stressors, and endocrine disrupters might impinge on the
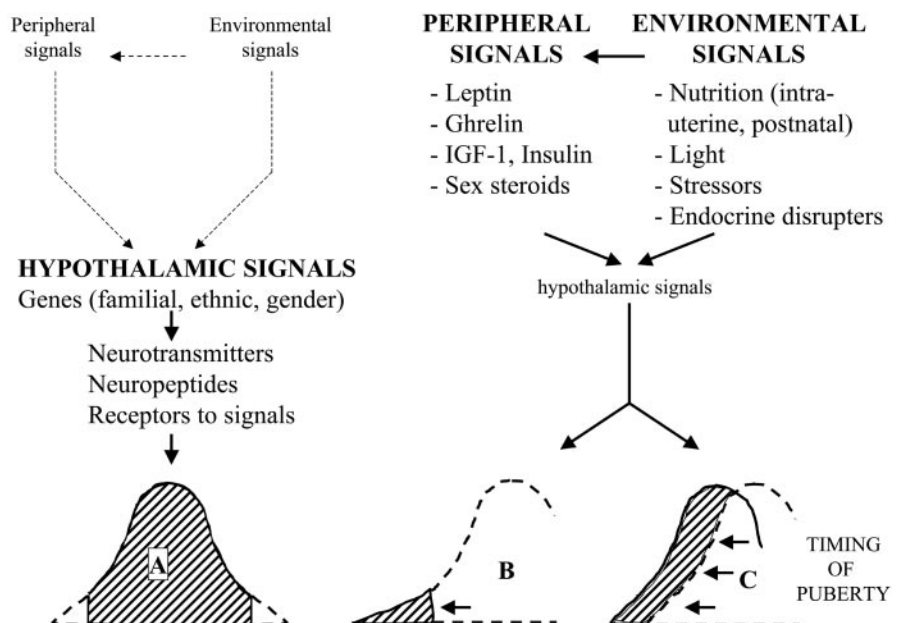
hypothalamic signaling network directly or through peripheral signals (Fig. 6). In the following sections, we will discuss the possible contribution of hypothalamic, peripheral, and environmental signaling to the differences in timing of puberty around the world and the early activation of the hypothalamic-pituitary-gonadal system in migrating children. It is, however, virtually impossible to isolate the contribution of each signal because many of them are interrelated. Geographical differences might involve altitude, temperature, humidity, and lighting. An underprivileged life setting might involve nutritional problems, high energy expenditure, insufficient public health, individual diseases, large family size, and social and emotional injuries.

A. Genetic factors (family, ethnicity, gender)

In 1935, Petri (127) reported a mean difference in menarcheal age that was 2.2, 12.0, 12.9, and 18.6 months in four groups of identical twins, nonidentical twins, sisters, and unrelated women. This finding and subsequent observations (3, 89, 128) derived from monozygotic twin correlation studies of menarcheal age indicate that 70–80% of the variance in pubertal timing can be explained by heritable factors. Using the maximum likelihood model-fitting method (129) and the survival analysis (130), two mathematical approaches that control for the biasing environmental influences in twin studies, the substantial role of genes in determining the timing of menarche was further strengthened. Kaprio *et al.* (3) used a bivariance twin ANOVA in menarcheal age and BMI. They concluded that 74% of the variance involved genetic (including dominance and additive) effects and 26% environmental effects. These data were consistent with the concept that, in privileged countries, there has been a possible secular increase in relative genetic effects on timing of puberty together with a decrease in environmental effects (129). Using a multivariate model for twin and longitudinal height data, Loesch *et al.* (131) calculated the absolute genetic contribution to the pubertal growth spurt,

which was found to be maximal at the time of peak height velocity. These data indicated the possible role of genetic factors in the individual differences in pubertal growth spurt with a gender dimorphism, possibly related to estrogen effects. In a recent review article, Palmert and Boepple (120) suggested that the genetic control of the variance in pubertal onset was likely to be a complex polygenic trait, and they proposed a study of the association with precocious or delayed variants in pubertal timing to unravel those genes. Similar genes could be involved in determining the timing of menarche and the risk of breast cancer later in life, thus accounting for the association between the two events. In pairs of monozygotic twins discordant for breast cancer, an earlier menarche did not predict an increased risk of the disease, whereas in twins concordant for breast cancer, an earlier menarche predicted an earlier occurrence or diagnosis of breast cancer (132). These data indicate that, in the heritable or familial forms of breast cancer, genetic susceptibility can cause unusual early sensitivity to sex hormones or unusual early load in sex hormones. Recently, two different polymorphisms of the estrogen receptor α gene, which were found previously to be associated with reduced breast cancer risk, were also associated with a relative delay in menarcheal age in Greek adolescent girls (133). More recently, in Japanese women, menarcheal age was found to be not associated with estrogen receptor α gene polymorphism. In contrast, early menarche was linked to the A2 polymorphism of CYP17 gene controlling androgen biosynthesis and thereby possibly accounting for increased serum estradiol levels (134). Such a polymorphism was also found to be associated with increased breast cancer risk in young women (135). In American girls, the CYP17 alleles were not associated with early breast development that was strongly associated with the A4 allele of CYP3, an enzyme involved in testosterone catabolism (136). However, no association between menarcheal age and polymorphic variants of the CYP3A4, CYP17, CYP1B1, and CYP1A2 genes was found in a Canadian cohort

FIG. 6. Schematic illustration of the relative influences of hypothalamic, peripheral, and environmental signaling on the physiological variability in timing of puberty (A) or the occurrence of a subset with sexual precocity (B) or the shift of the whole study population toward early pubertal timing (C).

Peripheral signals   Environmental signals

PERIPHERAL SIGNALS   **ENVIRONMENTAL SIGNALS**

- Leptin
- Ghrelin
- IGF-1, Insulin
- Sex steroids

- Nutrition (intra-uterine, postnatal)
- Light
- Stressors
- Endocrine disrupters

HYPOTHALAMIC SIGNALS
Genes (familial, ethnic, gender)

hypothalamic signals

Neurotransmitters
Neuropeptides
Receptors to signals

A   B   C

TIMING OF PUBERTY

of 583 healthy women aged 17–35 yr (137). Taken together, these findings suggest the involvement of genes controlling sex steroid biosynthesis, action, and metabolism in the genetic determinants of the timing of puberty with possible variations between countries and populations. This area is particularly complex because there are multiple mechanisms and sites potentially involved in sex steroid effects. The estrogen receptors are expressed in numerous tissues and might regulate many peripheral and central processes in the hypothalamic-pituitary-gonadal axis and their peripheral target tissues (138, 139). The androgen receptor gene can also be involved in the pathogenesis of pubertal disorders because a CAG repeat polymorphism was shown to be associated with ovarian hyperandrogenism (140).

It is likely that a cascade of genes may determine variations in timing of pubertal onset. In the rat, manipulation of some homeobox-containing genes (OCT2, TTF-1) involved as regulators of downstream genes of neuropeptides stimulating GnRH secretion such as TGFα, can result in alterations of the timing of puberty (141). We have not yet identified, however, the upstream genes that possibly mediate variations related to ethnic and familial patterns of development, as well as the striking sexual dimorphism in onset of puberty. Unraveling those genes will be critical because genetic control can account for most of the physiological variations in pubertal timing whereas peripheral and environmental signals could play relatively minor roles in that respect (Fig. 6A).

The ethnic or racial characteristics belong to the genetically determined factors and could contribute to the sexual precocity of foreign migrating children, in addition to environmental factors. In this respect, studies in migrating people provide an interesting model and put emphasis on environmental factors. In 1942, Ito (142) reported that, in Japanese girls born and reared in California, menarcheal age was more than 1.5 yr earlier than in Japanese girls born in California or Japan and reared in Japan. Although this study put emphasis on environmental factors, the dominant role of genetic factors was emphasized by others who found a similar menarcheal age in Turkish girls living in Germany in comparison with girls living in Turkey (143). Foreign adoption creates a unique situation with children from many different countries and races sharing a similar new setting, although many variables such as importance of former deprivation or insults and age at adoption still account for heterogeneity. In the Belgian experience, sexual precocity could not be related to any clear racial factor because the patients came from different countries all around the world and belonged to different races (17). The percentage of girls seen and treated for precocious puberty was relatively high (1.2%) among those coming from Colombia and India or Sri Lanka compared with other countries. There is a possible bias, however, because adoption from those countries has occurred for many years and at a relatively stable rate throughout the entire study period, whereas that from some other countries (Vietnam, China, Haiti) has started more recently and is still increasing. For instance, many patients with sexual precocity were seen from Haiti in the past few years but not formerly. In addition, differences among countries, such as absence of sexual precocity in girls adopted from Ethiopia or the Philippines, might involve racial and environmental influences, which

will be difficult to isolate from each other. In Western Europe, we have relatively few children adopted from Eastern Europe, whereas these countries, particularly Russia and Romania, have provided a great number of children adopted in the United States (119, 123, 144) and among whom early puberty was also common (119, 123). Thus, although racial factors may play some role in the timing of puberty, such a role is relatively minor and unlikely to explain the variations seen in different countries around the world or in migrating children (89).

B. Intrauterine conditions

It has been proposed recently that the intrauterine milieu might influence physiological and pathological events occurring throughout life, although the mechanism of such a programming remains elusive (145). With respect to puberty and reproduction, low birth weight appears to be associated with precocious pubarche (adrenarche) and ovarian hyperandrogenism in the human female (146) and subfertility in the male (147). Evidence of central precocious puberty associated with IUGR has been provided in some patients with Russel-Silver syndrome (148) because, in a review of 148 observations with data on pubertal timing provided for 17 girls and eight boys, eight girls and one boy showed early puberty (149). More recently, precocious puberty was reported in some IUGR patients with maternal uniparental isodisomy of chromosome 14 (150, 151). It is unknown why some particular patients with this syndrome or Russel-Silver syndrome will enter puberty early. Some variations in menarcheal age can be related to low birth weight. In the United Kingdom, the age at menarche was 0.2 yr earlier in girls with birth weight below 2.85 kg compared with those weighing more than 3.75 kg (152). Among Spanish girls with early puberty (B2 between 8 and 9 yr), menarcheal age was 1 yr earlier in girls with a birth weight below 2.7 kg compared with the rest of the cohort (153). In a recent study from Israel, the mean menarcheal age of IUGR girls was found to be advanced by 1.3 yr *vs.* girls with birth weight appropriate for gestational age, due to increased prevalence of early puberty and reduced prevalence of delayed puberty (154). In a French study, however, IUGR was found to be associated with a pubertal delay averaging 0.8 yr in girls and 2.1 yr in boys, respectively (155). In the general population, some authors found no significant correlation between birth weight and menarcheal age (156), whereas others reported that thin newborns enter puberty earlier (157, 158). A sexual dimorphism in the relationship between birth weight and timing of puberty was observed in a limited group of 35 girls who showed pubertal age positively and significantly correlated with birth weight tertiles, whereas a trend toward a negative correlation was seen in 34 boys (159). The female predisposition to early onset of puberty in IUGR (149, 159) is consistent with the gender dimorphism seen in other etiological conditions. This suggests that factors linked with IUGR are superimposed to a more general mechanism making females prone to develop sexual precocity. Experimental data obtained in rats of both sexes, indicate that IUGR causes delayed puberty in both sexes, whereas early postnatal malnutrition does not affect timing of puberty in the female but

causes a delay in the male (160). Thus, alterations in intrauterine conditions are possibly associated with disorders of puberty and reproduction, but their role in physiological variations in timing of puberty remains uncertain.

Could IUGR contribute to sexual precocity in adopted children migrating to Western Europe or the United States? In these children, the likelihood of increased incidence of IUGR is suggested by the Swedish cohort study in which 80% of 37 children with known birth weight were below 2.5 kg (161, 162). Unfortunately, information on birth weight and maternal risk factors for IUGR is lacking in the other studies. In those cases, we can only speculate until collaborative studies are set up between foster and home countries of adopted children. There is no evidence that, in the foreign adopted girls with precocious puberty, a putative IUGR can be linked with premature pubarche as observed in other female populations (146). By contrast, we reported that the development of pubic hair was less advanced in these patients compared with Belgian native girls with idiopathic or organic sexual precocity (163). This finding is consistent with the dissociation between adrenarche and gonadarche (21, 22). The delay in pubic hair development in migrating girls may involve particularly the subset of Indian girls, indicating a possible racial or geographical factor.

C. Nutrition

Among the factors linked with the living standards that account for the downward secular trend in timing of puberty and the differences between underprivileged and privileged settings, nutrition is likely to play a key role. This area appears to be most complex for the following reasons. 1) Nutrition involves both quantitative and qualitative aspects that have been rarely individualized in human studies. 2) Usually, the dietary status is assessed indirectly and incompletely through anthropometry. Weight and the related variables provide some information on storage of metabolic fuels, depending on individual differences in energy balance that may be genetically determined. 3) Reproduction has been more extensively studied than onset of puberty, whereas these two manifestations of pituitary-gonadal function can be differently affected by nutritional signaling. 4) The hypothalamic mechanism controlling food intake/energy balance and onset of puberty/reproduction involves common local and peripheral regulators, which are numerous and act through redundant pathways. 5) The contribution of differences in nutrition to disorders of puberty and reproduction does not mean that nutrition is a determinant of physiological variations in timing of puberty. In this section, we will concentrate on the possible involvement of nutrition in differences in timing of puberty around the world and in migrating children.

A direct relationship between body weight and the age at onset of puberty was suggested by Frisch and Revelle (164, 165) based on comparison between early and late maturers. Frisch *et al.* (166) concluded that a critical amount of body fat was needed for the onset of puberty. The maintenance of cycling in women has been estimated to require that at least 22% of body composition is fat (167, 168). In the amenorrheic running female monkey, ovulatory cycles are restored by increasing energy availability (169). However, the nutritional determinants of the ovulatory cycle can be different from the control of pubertal timing. The secular decline in menarcheal age occurs together with an opposite trend for regular cycling because, within a 25-yr period, the interval between menarche and regular cycling has increased from 1.9 to 3.0 yr and attains an interval of 5 yr in 21% of women instead of 9% formerly (170). These authors pointed out the possible influence of nutritional changes as well as differences in physical activities among female adolescents. Parallel to the delay in regular cycling, the prevalence of ovulatory disorders seems to increase, pointing to a possible environmental effect as well (171). Nutritional factors also play some role in polycystic ovary syndrome that can, however, predominantly involve genetic factors (172).

The Frisch and Revelle hypothesis has triggered a number of studies that confirmed (41, 156, 173–175) or did not confirm (28, 176–178) a significant relationship between menarcheal age and fat mass estimated through BMI or the sum of skinfold thickness or dual energy x-ray absorptiometry. It is debatable whether the Frisch and Revelle hypothesis could be relevant when only the physiological variations in body fatness are considered. As an example, girls with early menarche are more likely to be obese than those with late menarche (156), and, in comparison with nonobese girls, the average menarcheal age of obese girls was 9 months earlier in Japan (67) and 0.9 yr earlier in Thailand (179). However, the mechanisms involved in these pathological conditions may be different from those in normal subjects. Another difficult issue is the meaning of a significant correlation between fatness and menarcheal age. This may indicate a direct relation between fatness and menarche that can be either causal or consequential. Alternatively, the link between the two parameters can only be indirect because they share similar genetic determinants. In this respect, the recent study by Wang (180) is interesting because early sexual maturation is associated with an increased prevalence of fatness in girls and leanness in boys. Such a sexual dimorphism could involve genetic and/or endocrine factors. Several authors reported that early menarche was associated with an increased risk of obesity in adulthood (181, 182). Conversely, several studies suggested that childhood might be a critical period for weight to influence the timing of puberty because menarcheal age was inversely related to weight at 7 yr (152). Qing and Karlberg (183) reported that a gain in 1 U of BMI between 2 and 8 yr was associated with an advancement of age at the pubertal growth spurt reaching 0.6 yr in boys and 0.7 yr in girls. Davison *et al.* (184) reported that early onset of breast development by 9 yr could be weakly but significantly predicted by a higher percentage body fat at 5 and 7 yr. In this study, up to 14 and 35% of girls reached B2 stage at 7 and 9 yr, respectively, which was assessed, however, by visual inspection only. Kaprio *et al.* (3) suggested that the association between relative body weight and menarcheal age was primarily due to correlated genetic effects, whereas the two parameters were influenced by separate environmental correlates independent of each other. Karlberg (158) came to a similar conclusion about peak height velocity and menarche, which can occur simultaneously or at a time interval of 2 yr. They also emphasized the halt in secular trend in menarcheal

age while height (and weight) are still increasing. It is tempting to conclude that the link between nutritional status and physiological variations in timing of puberty can be significant but is not particularly strong, suggesting that the relationship is indirect or partial and superseded by other factors.

Is there any possible link between the anthropometric data and the ethnic variations in pubertal timing? In some studies, only a minor advancement of 0.1–0.3 yr in menarcheal age was observed in African-American girls as compared with white American girls (35, 41). That advancement was found to be 0.4 yr in the NHANES III cohort (39) and reached 0.7 yr in the PROS study (6), which raised the question of whether racial differences in nutrition and weight for height play any role. Recently, Anderson *et al.* (40) found that the racial differences in menarcheal age were independent of differences in BMI. In another recent study, African-American girls were found to be fatter and sexually more mature than white American girls, a difference that was associated with increased levels of free bioavailable IGF-I (185). These data, however, are not comparable to the PROS study (6) because pubic hair, which was used as the marker of sexual maturation, may provide information on adrenarche but not gonadarche. There are additional ethnic differences, including higher insulin response to a glucose challenge among black *vs.* white subjects, lower resting energy expenditure, and perhaps less physical activity (186), without evidence, so far, of contribution to the racial differences in pubertal timing. Kaplowitz *et al.* (187) used the growth data from the PROS study (6) to calculate the sd scores (SDS) or Z scores of BMI. They found these scores to increase at the time of onset of breast development and concluded that the gain in BMI was predictive of onset of puberty and consistent with the racial difference in pubertal timing. Again, this conclusion raises the above debate about the causal or consequential nature of the observed correlation. In addition, there is a possible bias in these study conditions because BMI reference data from average maturers were used to calculate Z scores in early maturers. Likewise, in the recent report by Wang (180), the definition of overweight in early maturers using the BMI percentiles obtained in average maturers can involve a similar bias. If an increase in BMI occurs early as a possible consequence of early pubertal development, the reference data from average maturers provide inappropriately low values to calculate Z scores of BMI in early maturers. This may result in overestimation of BMI increase and can mistakenly lead to the conclusion that such an increase has a causal influence on pubertal onset.

Studies assessing directly the influence of dietary intake on the age at menarche have not shown any clear correlation between diets and timing of puberty. A weak but statistically significant correlation was found between early menarche and energy intake and expenditure (173). In contrast, high *vs.* low energy intake was associated with later menarcheal age in heavy Hispanic girls in California, which might have been caused by underreporting of the dietary intake in some groups (188). The protein source of food in early life could also influence the timing of puberty because a high animal *vs.* vegetable protein ratio at the ages of 3–5 yr is associated with early menarche, after controlling for body size (189).

Phytoestrogens in the diet might have a role in the regulation of puberty both directly and indirectly (190). They interact with estrogen receptors and may have either agonistic or antagonistic effects, depending on the endogenous hormonal balance (191). In prepubertal boys who have very low endogenous estrogen levels, phytoestrogens might have some agonistic effects, whereas antagonistic effects would be expected when endogenous estrogen levels are higher. It was shown in the rat that the phytoestrogen coumestrol caused both reduced frequency of the electrophysiological hypothalamic discharges associated with pulsatile LH secretion as well as direct pituitary inhibition (192). In addition to their receptor effects, phytoestrogens affect the metabolism of hormones. They have been shown to inhibit aromatase and 17β-hydroxysteroid dehydrogenase type 1 and type 5 enzymes (193–196). Thus, the sum effect of phytoestrogens appears clearly antiestrogenic, which is also in accordance with animal experiments (197). A phytoestrogen-rich diet might therefore delay puberty as demonstrated by Berkey *et al.* (189). Such a conclusion may be relevant to the nutritional changes that can be involved in early puberty after migration because vegetable products such as soybean or cassava are major food components in developing countries but not in Western European societies (198).

Underfed children have delayed puberty (199), and, in many children adopted from foreign countries, malnutrition at arrival has been reported. The mean SDS of weight for height at arrival was −0.6 in the Swedish study (161, 162), and the weight deficit was −10.5% in the Italian study (14). In such conditions, a catch up in height and weight is commonly seen after arrival and precedes early sexual maturation. This has led to the hypothesis that hormonal events linked with catch-up growth may prime hypothalamic maturation and lead to puberty. This hypothalamic priming was thought to possibly occur in a critical age window because precocious menarche (<10 yr) was more common in Indian girls who arrived in Sweden between 3 and 6 yr than in those who arrived before 2 yr of age (11). The concept of a critical prepubertal period for nutritional priming of maturation is in agreement with observations in healthy boys and girls (152, 183, 184). Proos (200) reported that, in foreign adopted children, earlier menarche was correlated with later age at immigration and faster catch up in height and weight after immigration. He found, however, in a multiple linear regression analysis, that menarcheal age was associated with height at immigration but not with age at immigration. In a study of 65 Romanian adoptees in the United States, Johnson *et al.* (144) found that only 15% of them were mentally and physically healthy at arrival. These authors observed that growth failure was directly correlated with duration of institutionalization, every 3 months of life in an orphanage resulting in a loss of 1 month in height age. They also reported that weight was usually less compromised than height, suggesting that nutritional deprivation might play a less prominent role than other factors such as genetics, prematurity, IUGR, medical illnesses, and stress. A catch-up growth was also noticed after adoption, with a greater extent of recovery in children adopted before 18 months than in those adopted at later ages (144).

Whereas the impact of nutritional deprivation and resto-

ration after migration may be crucial in some foreign children who develop sexual precocity, others have normal weight and height at arrival. In the French study, the mean SDS of weight for height of foreign adopted children was +1.2 at immigration (16). In the Belgian series, the mean SDS of BMI was −0.2 at arrival, indicating normal weight for height on average (17). The interpretation of height and weight data in adopted children, however, should be cautious because the Western European or North American references may not be applicable. In a study of Indian adolescent boys who showed peak height velocity at an average age of 13, which is similar to American boys, the prevalence of height and BMI below the fifth centile using the NCHS references was 11 and 50%, respectively (201). In addition, the proportion of obese and wasted children was not necessarily reciprocal, and variability among countries was considerable (202). Quite interestingly, the observation of precocious puberty in nonadopted foreign children migrating to Belgium together with their original families and without evidence of former nutritional or affective deprivation (17) provides further support to the role of factors other than nutrition in relation to the changing environment. To mimic catch-up growth after immigration in formerly deprived foreign children, early underfeeding and refeeding was used in the rat, and the effects were studied on hypothalamic glutamate neurotransmission, which is a major trigger of pulsatile GnRH secretion (1, 203). An acceleration of maturation of the glutamate receptor-dependent secretion of GnRH occurred after refeeding and was maximal at a particular postnatal age period (12). These data suggest the involvement of hypothalamic glutamate receptors in the pathophysiology of that form of sexual precocity.

Whether fat-derived signals, such as leptin, or body-size linked signals, such as IGF-I, or other factors related to energy availability, such as glucose, are essential for timing of puberty and regulation of reproduction remains a matter of debate (204, 205). Peripheral leptin signaling is likely to be permissive only in physiological conditions (Fig. 5), as suggested by the controversial studies throughout normal development in human and subhuman primates (205, 206). In some nonphysiological conditions, leptin appears to be a prerequisite to normal hypothalamic-pituitary-gonadal function (205, 207), confirming rodent studies (208–210). In girls with sexual precocity, controversial data have been obtained because modestly but consistently increased serum levels of leptin were observed by Palmert *et al.* (211), whereas no difference in BMI-adjusted levels was found by Heger *et al.* (212). Another recent candidate messenger between nutritional status/energy balance and the hypothalamus is ghrelin (213), which we found to be capable of stimulation of pulsatile GnRH secretion from prepubertal rat hypothalamic explants (214). In conditions with impaired and restored nutrition, other endocrine changes, such as increased secretion of IGF-I, may occur during catch-up growth and act as a mediator between the environment and the hypothalamus. Although a role of IGF-I has been advocated for many years, its contribution remains equivocal (215, 216). Acute effects of glucose on pulsatile LH secretion have been shown in the lamb (217), but not in the rhesus monkey (218). As reviewed by Cameron (219), different metabolic signals, including glu-

cose, insulin, and leptin, are capable of modulating reproductive axis activity under specific circumstances, but their physiological role remains unknown. A potentially important contribution of sex steroids in the hypothalamic effects of environmental signals is suggested by the reduced expression of hypothalamic estrogen receptors after food restriction (220, 221). Thyroid hormones can be a mediator of environmental effects as well (222). This indicates the complexity of the potential neuroendocrine interactions between nutritional conditions and puberty, including the role of estrogen receptors such as already discussed in *Section IV.A*. In addition, there are possible peripheral effects of some forms of undernutrition (kwashiorkor, anorexia nervosa) resulting in increased serum concentrations of SHBG which are reduced by refeeding and may affect the bioavailability of sex steroids (223, 224).

D. Other stresses

Different stresses, such as acute or chronic illnesses and adverse physical or psychological conditions, are known to depress the hypothalamic-pituitary-gonadal system (225, 226). Intensive physical training and sport competition, such as in elite gymnasts, can result in combined physical, psychological, and nutritional stresses that are associated with delayed puberty or late menarche (227, 228). In war conditions, which involve nutritional deprivation and psychological or emotional insult such as occurred in Bosnia and Croatia, a delay in menarcheal age or a reversal of the secular trend was observed (229, 230). In these chronic conditions, it is difficult to isolate the participation of each stress factor. Some acute stress situations may not result in observable effects on menarcheal age as shown in tribal girls undergoing female circumcision at adolescence (231). In another acute situation, such as fasting-induced suppression of LH secretion, metabolic signals were shown to play a more important role than psychological stress (232). The relative difference in impact of the components of a stressful situation is further suggested by the heterogeneity of the neuroendocrine response to various acute stressors, indicating that they are signaling through specific pathways (233). Among the neuronal circuits involved, signaling through CRH and IL-1 may be particularly important (234). Thus, it is possible that, in foreign migrating children, withdrawal from a stressful environment contributes to potentiation of maturation, although some stress may result from the adoption and migration processes as well. The latter hypothesis might be consistent with the observation of early pubertal development in conditions of stressful rearing and insecure attachment to parents (235, 236).

E. Light-darkness cycle and climatic conditions

Environmental signals related to climate and light deserve some attention in the context of variations in pubertal timing around the world, as well as migrating children with sexual precocity. Temperature and light-darkness rhythms that are influenced by geography and seasons might modulate the reproductive axis. As discussed above (Fig. 2), a north-south gradient in menarcheal age around the world has suggested

the possible influence of climatic conditions although most observations indicate that climate in itself has little or no effect on menarche (89). In Caucasian Jewish high school girls, menarche is earlier in the hot city of Elat than in the temperate city of Safad (237). In the 1950s, however, Zacharias and Wurtman (89) observed a similar menarcheal age in Nigerian (238) and Alaskan Eskimo girls (239).

Indirect evidence of a role of exposure to light in human puberty comes from the fact that blind girls have earlier menarche than normal (240, 241) although these reports were not confirmed subsequently. Several studies have suggested that menarche starts relatively more frequently in winter than in summer in normal girls (242–244), suggesting an inhibitory effect of photostimulation. However, in the Arctic area, the dark winter months may be associated with reduced pituitary-gonadal function and low conception rates (245). Thus, the influences of light and temperature on the human reproductive axis are uncertain and rather minor as compared with the seasonally breeding animals. The effects of light-darkness rhythms can be mediated through the pineal gland hormone, melatonin, which circulates in high concentrations at night. Melatonin is inhibitory to the neonatal rat pituitary gland (246), whereas its neonatal administration accounts for sexual precocity (247, 248). In man, because a fall in peripheral melatonin concentrations occurs during the peripubertal period (249–251), a role for melatonin in the onset of puberty has been proposed, which is further supported by observations in sexual precocity and hypogonadotrophic hypogonadism (252, 253). The most obvious decrease in melatonin secretion, however, occurs after onset of puberty, between Tanner stages II and III (251). This might suggest that melatonin secretion decreases as a consequence of increase in sex steroid levels at puberty, a concept further supported by studies in isolated gonadotropin deficiency and delayed puberty (254). The role of melatonin in human puberty warrants further longitudinal and mechanistic studies correlating melatonin secretion with other hormonal parameters. An influence of seasonal factors on sexual precocity in migrating children cannot be excluded at this point, although the average period of 4 yr between migration and early onset of puberty (17) is inconsistent with the time sequence of changes in melatonin secretion and puberty in normal children.

F. Exposure to endocrine-disrupting chemicals (EDCs)

EDCs are widespread environmental substances that have been introduced by man and that may influence the endocrine system in a harmful manner (255, 256). EDCs account for several disturbances in wildlife (257) and may also play a role (256, 258) in human disorders of sex differentiation and of reproductive organs and functions. Also, the possible role of EDCs in development of hormone-dependent cancers such as breast cancer is a matter of concern, although the data are controversial (259). Krstevska-Konstantinova and coworkers (17) have hypothesized that moving to Belgium could result in a change in exposure to EDCs when a child moves from the home country to the foster country, thus causing sexual precocity to occur. The screening for eight organochlorine pesticides in serum of foreign migrating patients with precocious puberty in comparison with Belgian native patients has revealed the presence of p,p'-DDE [1,1-dichloro-2,2-bis(4-chlorophenyl) ethylene] in migrating children (17). p,p'-DDE is a persistent derivative of the insecticide DDT [1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane] with a half-life of several decades. DDT has been banned in the United States and Western European countries since the late 1960s (104, 260) but is still used extensively in developing countries. DDT and some isomers behave as estrogen agonists and/or androgen antagonists (261, 262). In 26 foreign patients (15 adopted and 11 nonadopted) with precocious puberty, the mean serum concentration of p,p'-DDE was 10 times higher than the limit of detection, whereas the levels were below this limit in 13 of 15 Belgian native patients (17). Three of the foreign patients were born in Belgium and showed elevated serum levels of p,p'-DDE, suggesting a transplacental or lactational route of exposure. The latter hypothesis is consistent with the lipophilic nature and bioaccumulating capacity of DDT and other widespread endocrine-disrupting compounds such as polychlorinated and polybrominated biphenyls. Also, the possible relationship between sexual precocity and fetal or perinatal exposure to EDCs is raising the issue of the period of exposure during development, a possibly critical parameter (263, 264). Recently, a 32% fall in probability of pregnancy in 28- to 31-yr-old daughters was found to be associated with 10 μg/liter of p,p'-DDT in mother's serum drawn around the time of delivery (265). Although the mechanism underlying such an association is unclear, it indicates the importance of very long-term studies, as in the case of diethylstilbestrol (266). In the Belgian study (17, 267), it was likely that the p,p'-DDE levels resulted from contamination in the country of origin because they were correlated positively with age at immigration and negatively with time since immigration (Fig. 7). However, in addition to DDT contamination in the country of origin, exposure to other EDCs in both the country of origin and the foster country is quite likely and should be considered in the mechanistic approach. This is a most difficult issue because the number of potential EDCs is increasing dramatically in the environment, and isolation of the responsible agent or mixture of agents is usually not possible. As an example, it was reported very recently that a blood lead concentration of 3 μg/dl was associated with delayed breast and pubic hair development in black American girls but not in white girls (268). Another recent study came to slightly different conclusions because increased lead levels were associated with delayed pubic hair and menarche but not with breast development in a mixed cohort of American girls (269). In migrating children, the link between DDT and sexual precocity is only correlative at this point, and DDT contamination is an expected finding in any child migrating from a developing country. Thus, the demonstration of DDT involvement in the pathogenesis of sexual precocity warrants further comparison with foreign migrating children who had normal or even delayed puberty. In addition to the estrogenic effects of EDCs, they may also cause antiandrogenic effects that could explain the delay in pubic hair development (see above), although ethnicity may play a role as well.

A pathophysiological mechanism of sexual precocity can be proposed (Table 4), based on exposure to estrogenic EDCs in the
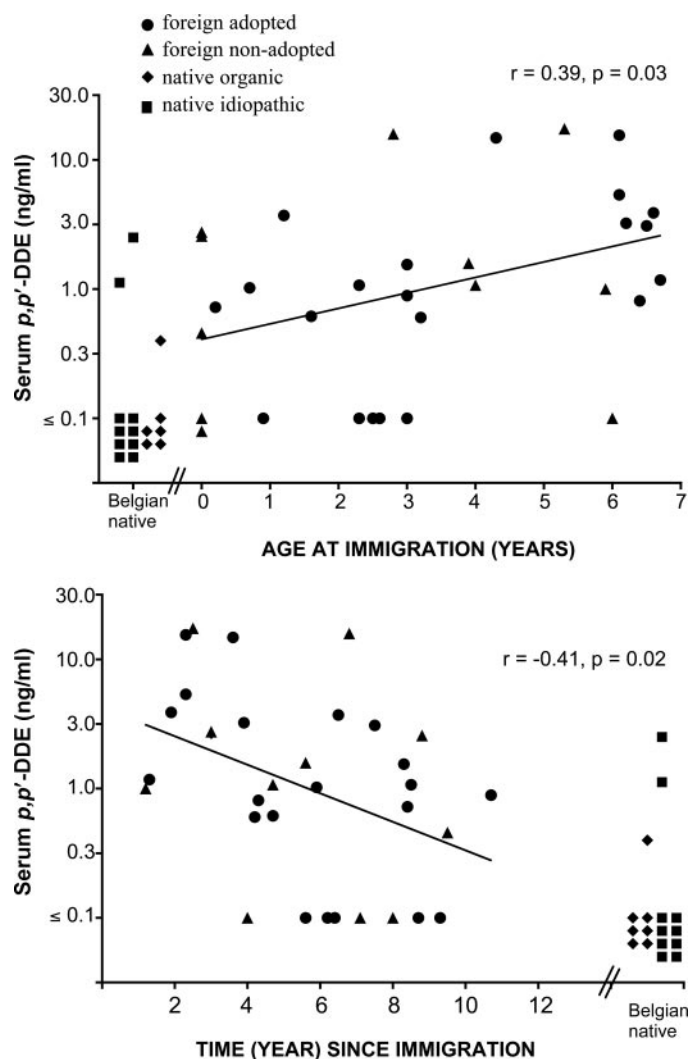
FIG. 7. Serum levels of p,p'-DDE, a derivative of the organochlorine pesticide DDT in different patients with sexual precocity. The Belgian native patients have central precocious puberty of organic or idiopathic origin. The foreign migrating patients with sexual precocity are adopted or nonadopted. The data of foreign patients are represented in relation to age at immigration and time since immigration.

country of origin and withdrawal after migration to Western Europe. Three other conditions provide analogies with the sexual precocity in migrating children. In congenital adrenal hyperplasia (270, 271) or peripheral isosexual precocity secondary to tumoral (272) or gonadotropin-independent secretion of sex steroids (273, 274), there are common consequences of exposure to sex steroid effects. It is well known that sex steroids exert a central inhibitory or negative feedback effect on the hypothalamic-pituitary-gonadal system to which the prepubertal subject is most sensitive (9). The predominant pituitary inhibition by estradiol has been recently confirmed by the increased gonadotropin secretion after the administration of an aromatase inhibitor to early pubertal boys (275). Such an inhibition may explain why precocious puberty does not necessarily occur in the country of origin where exposure to estrogenic EDCs is sustained. Obviously, the exposure to sex steroid effects may result in peripheral signs of feminization or virilization depending on the nature, potency, and duration of the involved

steroid. Also, it is possible that steroids interact with the neuroendocrine system to promote hypothalamic maturation. Such an effect is suggested by preliminary data obtained using hypothalamic explants from immature female rats and showing acceleration of pulsatile secretion of GnRH *in vitro* by estradiol and some DDT isomers (267). Additional evidence has been provided very recently by the estradiol receptor-mediated stimulatory effects of two organochlorine pesticides on GnRH nuclear transcripts in cultured immortalized GnRH neurons (276). The therapeutic interruption of exposure of the prepubertal patient to adrenal or gonadal sex steroids may, secondarily, result in central precocious puberty. Likewise, migration may interrupt exposure of foreign children to some EDCs. In such conditions, it is unknown whether central precocious puberty could result indirectly from withdrawal of the negative feedback effects of the sex steroids or their environmental analogs and/or directly from accelerated hypothalamic maturation caused by sex steroids. The dosage of estrogens or biopotency of EDCs may play an important role because it was shown that spermatogenesis was delayed or advanced after neonatal administration of high or low doses of diethylstilbestrol (277). According to the above-mentioned hypotheses, sexual precocity in migrating children is ultimately of central origin but may initially involve a peripheral (environmental) trigger, with reference to the primary cause. Thus, this condition may point to a new central effect of environmental hormones, in addition to their well-known peripheral gonadotropin-independent manifestations of sexual precocity (104, 278). In agreement with this concept, early menarche was reported recently in girls who showed an epidemic breast development between 3 and 7 yr of age, presumably resulting from transitory EDC contamination of some food served at school (279). According to the withdrawal hypothesis discussed above, sustained exposure to exogenous steroids or EDCs could result in delayed puberty through pituitary inhibition. Such a concept is consistent with the recent findings of Den Hond *et al.* (280) who studied 17-yr-old boys more or less exposed to polychlorinated biphenyls in a Belgian industrial setting. They found that 38–52% of the more exposed adolescents, as shown by serum polychlorinated biphenyl concentrations, had not yet attained the final stage of genital and pubic hair development as opposed to 0–23% of the less exposed subjects. In girls exposed to polycyclic aromatic hydrocarbons (dioxin-like compounds), breast development was delayed, but menarcheal age (mean, 13.1 yr) was not affected (281). Taken together, these data might be consistent with pituitary inhibition and/or peripheral antagonistic effects.

Sexual precocity has been reported rarely in foreign children adopted in the United States, although up to 140,000 children were adopted in this country from foreign countries between 1960 and 1990 (200) and 100,000 between 1990 and 2000 (123). It could be argued that the revised limits for sexual precocity in the early 2000s may have accounted for recent underreporting, but it is difficult to understand why there were no, or only anecdotal, reports in the preceding decade, after the problem was reported in Europe in the early 1990s (11, 12). Before the abstract and review reports published recently in the United States (119, 123), we hypothesized that possible differences in EDC contamination in Western European countries and the United States might explain differences in occurrence of sexual precocity. This

TABLE 4. A withdrawal hypothesis of central precocious puberty (CPP) after prepubertal exposure to sex steroids

Condition	Reason of exposure	Reason of withdrawal	Ref.
Congenital adrenal hyperplasia	Diagnostic or treatment failure	Treatment adequacy	270, 271
Peripheral precocity (tumors)	Secretion of sex steroids	Surgery	272
Peripheral precocity (McCune Albright syndrome)	Autonomous secretion of sex steroids	Treatment	273, 274
Exposure to xenoestrogens	Living in a contaminated setting	Migration	17

Target tissues	Consequences of exposure	Consequences of withdrawal	Ref.
Hypothalamus	Silent accelerated maturation?	Expressed accelerated maturation	267, 276
Pituitary gland	Inhibition (negative feedback)	Reduction or suppression of negative feedback	9, 275
Peripheral (breast, pubic hair, . . .)	Variable feminization or virilization	Secondary CPP	270–273

hypothesis cannot be denied so far because there have been no systematic and prospective studies on pubertal development in relation to possible exposure to EDCs in native and foreign migrating children. Such studies should be planned urgently by an international network of scientists.

V. Conclusion and Future Research Directions

The variations in age at onset of puberty involve different components including the average timing, the pattern of age distribution, and the variability, which is the difference between average and upper/lower age limits. The differences in average timing of puberty among countries around the world have become relatively small because they do not exceed 1 yr in well-off conditions, and the secular trends have been less marked than before the 1960s except in conditions of undernutrition. In contrast, an important individual variability in physiological pubertal timing that attains 4–5 yr is consistently seen despite optimal or improved living standards in most countries. In addition, new forms of sexual precocity are seen, such as in children migrating from developing countries. As summarized schematically in Fig. 6A, this individual variability, which involves familial, ethnic, and gender patterns, is likely to depend on the genetic control of the expression of signals or signal receptors in the hypothalamus. This process is only slightly influenced by peripheral and environmental signals, which play an essentially permissive role in those conditions. In specific situations, however, these peripheral and environmental signals may play a crucial role in the occurrence of either abnormal precocious (or delayed) puberty in a subset of a population (Fig. 6B) or increased incidence of precocity (or delay) because of a shift in timing of a whole population (Fig. 6C). The latter situation is consistent with the recently demonstrated advancement in onset of breast development in the United States, where revised limits for sexual precocity were proposed. No similar changes were evidenced in Europe, where the age criteria for precocious puberty have remained unchanged. Whether such discrepant observations involve differences in nutrition or living standards and/or the recently postulated effects of endocrine disruptors remains to be elucidated. A challenging observation that put emphasis on the environmental factors is the overall early age at onset of puberty and the increased incidence of sexual precocity in foreign children who migrate from developing countries to Western Europe and, probably, to the United States as well.
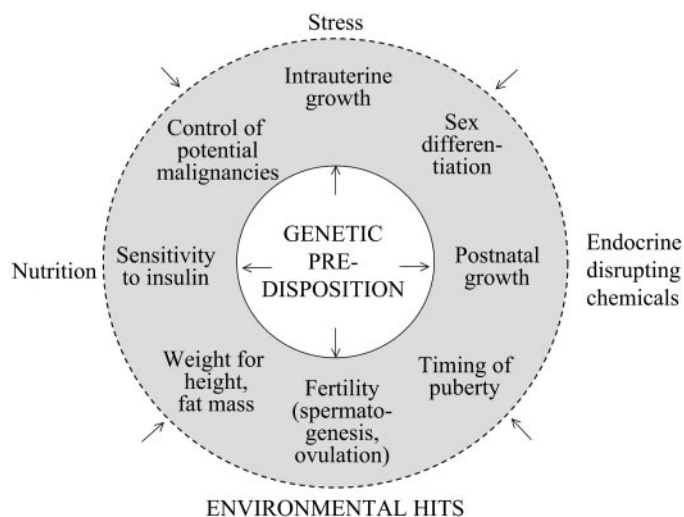

FIG. 8. Integration of timing of puberty within a spectrum of processes that are influenced by both genetic and environmental factors. This concept may explain the nonfortuitous association of disorders in the testicular dysgenesis syndrome described in the male (258) and the polyendocrine-metabolic syndrome in the female (146).

However, there is no simple and single explanation to this phenomenon. Further studies should evaluate the effects of migration by comparing the timing and dynamics of pubertal development in both the developing and developed countries. A combination of epidemiological, toxicological, and endocrinological studies is warranted to better delineate the possible role of EDCs because precocious puberty in migrating children may represent an additional example of the undesirable effects of emerging environmental chemicals. In a broader sense, this review has integrated timing of puberty and its disorders within a spectrum of physiological processes or diseases throughout life (Fig. 8). Several more or less strong associations have been observed between intrauterine growth, sex differentiation, pubertal timing, fertility, fat mass, sensitivity to insulin, and cancer risk. Nonfortuitous associations of disorders involving these processes have been proposed as the testicular dysgenesis syndrome in the male with hypospadias, cryptorchidism, reduced sperm count, and testicular cancer *(258)* and a polyendocrine-metabolic syndrome in the female with IUGR, precocious pubarche, ovarian hyperandrogenism, ovulatory dysfunction, hyperinsulinism, and dyslipemia (146). Such associations may be determined by both genetic factors and environmental hits

that may be common to some of those manifestations. Along this line, the timing of puberty may be one early sensor of the effects of genetics and environment, these two components being often combined. This is a continuing challenge for both researchers and clinicians.

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Important Dates

April 1st, 2004	Deadline for Abstracts Submission
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