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Growth and Puberty
Secular Trends, Environmental and Genetic Factors

A Collective Expert Report

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Institut national de la santé et de la recherche médicale

(National Institute for Health and Medical Research)

This document presents the work conducted by the group of experts brought together by Inserm within the scope of the collective expert report procedure (Appendix) in response to the request expressed by the RSI [Régime social des indépendants (Social Security Scheme for the Self-Employed), formerly Canam] concerning growth and puberty, secular trends and potentially influential environmental and genetic factors.

This work is based on the scientific data available during the second quarter of 2006. Almost 350 articles have served as the documentary basis for this expert report.

This collective expert report has been coordinated by the Inserm Collective Expert Report Center.

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Foreword

Ever since the XIXth century, European children have been growing and developing faster, becoming taller and maturing earlier. Secular trends in Europe are clearly linked to industrialization and changes related to lifestyle, hence these modifications did not occur simultaneously in the various European countries.

The halt in changes currently observed in certain countries throughout Europe must be interpreted on the basis of all the socio-economic and nutritional factors. Have living conditions ceased to improve? Or are environmental conditions less favorable? Or have conditions reached such a level of quality that the genetic potential is optimally expressed?

Regular evaluations of growth status in a population are still important because they are an appreciable public health resource. In France, there are no recent representative studies of the general population highlighting transversal or longitudinal data.

At the same time, most western countries are witnessing a constant increase in childhood obesity and a lowering of the age of onset of puberty. A certain number of epidemiological studies appear to indicate a probable correlation between these phenomena. However, the direction of the correlation has yet to be determined. Finally, observational studies have highlighted individual changes in relation to the impact of stress on growth and reproduction, and experimental studies aim at clarifying the mechanisms involved.

Canam, which became the Régime Social des Indépendants (RSI) (National Social Security Scheme for the Self-Employed), asked Inserm to carry out a collective expert report on the subject of growth, puberty and related trends in order to identify useful areas to explore in public health and fundamental research.

To this end, a group of experts was created; they analyzed recent studies on these topics, adhering to the following question framework:

. What trends have been observed as concerns growth and the age of puberty in recent years? What factors are involved? How are these parameters (height and age of puberty) public health indicators?

. What the determining genetic and environmental factors involved in growth and the onset of puberty in individuals and populations as a whole? What are the interactions between environmental and genetic factors in normal and pathological development?

. What role does leptin play in growth and the onset of puberty in boys and girls? How should the link with obesity be explained?

. What principal neurobiological mechanisms are involved in the onset of puberty? What could be the new clinical and laboratory markers for highlighting premature phases of puberty?

. How can the influence of premature stress on puberty and growth be highlighted?

After analyzing international published data on this topic, the group of experts summarized the key messages and proposed research recommendations.

Summary

Epidemiological studies highlight the influence of environmental factors on growth (height) and maturity (age of puberty) in a population. They are used to identify children who are either above or below the norm. It is generally admitted that changes in environmental conditions, particularly nutrition, are the main causes of secular changes in height during adulthood.

The links between secular trends in adult height and height at puberty have been widely investigated in recent years. A particularly significant lowering of the age of menarche is observed in most western countries. However, inter-individual variability may reach 4-5 years and depend on genetic and environmental factors and probably on the interactions between both types of factors.

Numerous studies indicate the close correlation between adipose mass and puberty. Overweight girls reach sexual maturity earlier than slim girls. This, however, raises the question as to whether excess weight induces premature sexual maturity or, on the contrary, whether early sexual maturity *per se* triggers excessive weight gain. Conversely, studies show a negative correlation between adipose mass and sexual maturity in boys. Studies currently underway aim at clarifying the role of leptin in relation to adipose mass in normal sexual maturation in both boys and girls. Although the initial signal of puberty has not yet been elucidated, the sequence of major hormonal changes can be investigated in animals. Animal models can also be used to investigate the effects of premature stress on the principal endocrine axes involved in growth and pubertal development.

Secular growth trends

Epidemiological growth studies are essential for evaluating the influence of environmental factors and for identifying the health status of an individual and a population. In individual terms, growth surveys can highlight children who are either above or below the norm. These surveys broach problems as diverse as obesity, nutritional deficiencies, genetic diseases or syndromes, socio-economic differences and even the impact of psychological factors.

A detailed growth and development analysis is based essentially on longitudinal data, i.e. serial data for the same subject, thus allowing the individual growth curve to be plotted. These data can, for instance, be used to evaluate growth rates and consequently, growth dynamics.

Most of the population growth studies are transversal, i.e. they are carried out on the basis of single measurements recorded in various subjects at each age. The results of these transversal studies can be used to estimate the central trends in a population and the variation in growth data at each age. These transversal data also provide the basis for establishing normal growth (or reference norms) illustrating "average" growth and the limits of "normal" variation in a population. These transversal growth studies are, therefore, interesting both at an epidemiological level and in terms of analyzing the influence of genetic and environmental (in the broadest sense of the term) factors.

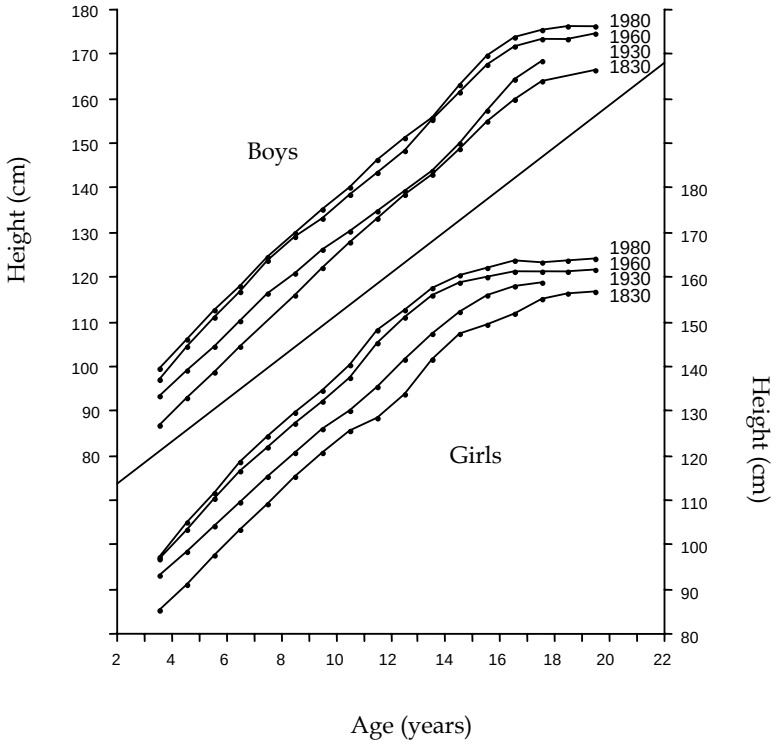
France has no recent transversal or longitudinal reference data. The reference curves generally used are those plotted in the study conducted by Sempé *et al.* and published in

1979, focusing on children born between 1953 and 1960, and monitored for 21 years. There are no recent transversal or longitudinal studies of data relating to children born after the 1960s.

We know that changes in growth patterns linked with processes of industrialization and modernization are evident in all European countries. These are so-called secular changes, which have been observed since the XIXth century, characterized by faster growth and development, greater average heights and precocious maturity. The phenomenon does, however, vary from one country to the next and does not develop in a linear fashion. At the present time, secular trends in height at adulthood are slowing down and have even ceased in some European countries such as Belgium, for instance. There may be two reasons for this deceleration – either optimal environmental conditions have been reached for complete genotype expression or environmental conditions have ceased to improve in recent decades.

With the secular trend in height, it is normal to witness changes in weight in both children and adults. From the 1980s onwards, a tendency towards a relative weight increase seems to reflect the growing epidemic of obesity observed in the western world.

In Europe, the secular trend in growth pattern is clearly associated with industrialization and changes in lifestyle. This explains why secular changes did not simultaneously occur in the various European countries - in the XIXth century in England and Belgium, for example, not until the early XXth century in France and even later in Spain.



Secular trend in the height of boys and girls in Belgium (according to Vercauteren, 2003)

These differential trends are also due to geographical variations. An analysis of the average height of males per *département* in France shows a considerable interdepartmental heterogeneity with a northeast to southwest gradient, with the tallest males being recorded in the north and northeast compared and the shortest in the south and southwest. Furthermore, a greater increase was observed between 1960 and 1989 in *départements* where

an average shorter height was initially recorded, thus resulting in diminished interdepartmental heterogeneity in 1989. However, more recent results are not available.

It is generally admitted that the changes observed in growth and development are good indicators of living conditions in a society, and particularly of nutritional status and health. The secular trend manifests the living conditions of a population and also highlights any imbalance in health trends within the same population. Regular measurements of the growth status in a population are, therefore, important since they are an appreciable resource for analyzing public health.

Secular trends in the age of puberty

Growth during puberty accounts for 15 to 20% of the height reached at adulthood. Links between the secular trend in adult height and that at the age of puberty have been widely investigated in recent years. Various genetic and environmental factors have been explored for their correlation with the age pubertal development.

Puberty corresponds to the activation of the hypothalamo-hypophyseal-gonadal function resulting in the full development of sexual characteristics, the final height, reproductive function and fertility. Different stages in pubertal development are defined according to the Tanner classification, focusing on secondary sexual characteristics.

Tanner classification of the stages in pubertal development

Stages in the pubertal development
Pubic hair growth in boys and girls
P1 No pubic hair at all P2 Small amount of long pubic hair P3 Pubic hair growth above the pubic symphysis P4 Established pubic hair growth P5 Hair growth spreads to the surface of the medial thigh, extending towards the navel in boys
Development of breasts
S1 or B1 No breast development S2 or B2 Small breast bud with enlargement of areola S3 or B3 The breast gland exceeds the area of the areola S4 or B4 Maximum development of the breast (appearance of a fold underneath the breast), projection of the areola and papilla (nipple) above the gland S5 or B5 Adult appearance, disappearance of projection of the areola
Development of external genitalia in boys
G1 Infantile testicles and glans penis G2 Increase in testicular volume from 4 to 6 ml (L 25 to 30 mm) G3 Continuation of testicular growth from 6 to 12 ml (L 30 – 40 mm), increase in glans penis G4 Testicular increase from 12 to 16 ml (L 40 – 50 mm) and increase in glans penis G5 Adult morphology

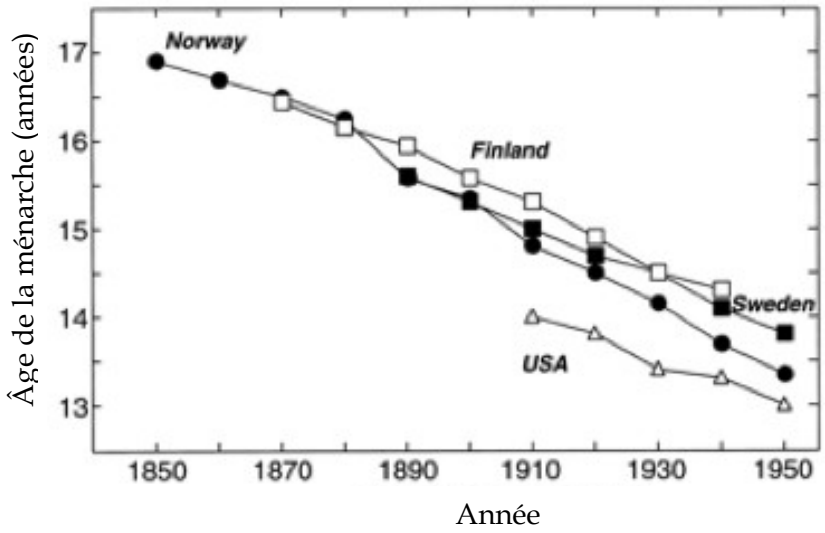
In girls, the first sign of puberty is the development of breast glands, which starts on average around 10.5 /11 years of age. This is followed by the growth of pubic and axillary hair, changes of the vulva and finally the onset of menstruation (menarche), which generally occurs around the age of 13, some 2 to 2.5 years after the first signs of puberty. The date of onset of menarche is considered physiological between 10 and 15.5 years of age. Puberty in

girls occurs with a bone age of 11 years (10 to 12 years) corresponding to the appearance of the sesamoid bone of the thumb.

In boys, the first sign of puberty is an increase in the volume of the testicles, which on average occurs between 12 and 13 years of age. The other signs of pubertal maturity are pubic and axillary hair growth and an increase in the size of the glans penis. Puberty in boys occurs with a bone age of 13 years corresponding to the appearance of the sesamoid bone of the thumb.

An estimation of the average age of puberty in a population raises various methodological problems mainly associated with data collection methods and the stages in question. In Europe, menarche begins at 12 years of age in Italy, 12.6 in France and 13.5 in Germany. As regards boys, various American and European studies concur on an average age of 11.6 years for stage G2.

Between the mid XIXth and XXth centuries, the average age of menarche substantially fell from 17 to 14 years in the United States and in several Western European countries. The curve of this trend nevertheless varies from one country to the next: a decrease of 0.3 years per decade was calculated on the basis of Norwegian and Finnish data as well as in prospective American studies. A decrease of 0.175 years per decade is estimated in France.



Secular trend in the age of menarche in 4 countries

The existence of a north-south gradient in the XIXth century should be noted with a lower age of menarche in Southern European countries (France) than in Northern countries (Scandinavia). However, studies carried out in these countries after 1960 tend to show a stabilization or even a halting of this trend.

In other countries, however (India, China and Bulgaria), the decrease is just as marked as it was in western countries prior to 1960. These trends are consistent with changes in living conditions in the various countries. The secular trend in the age of menarche seems to be associated with the increase in the body mass index.

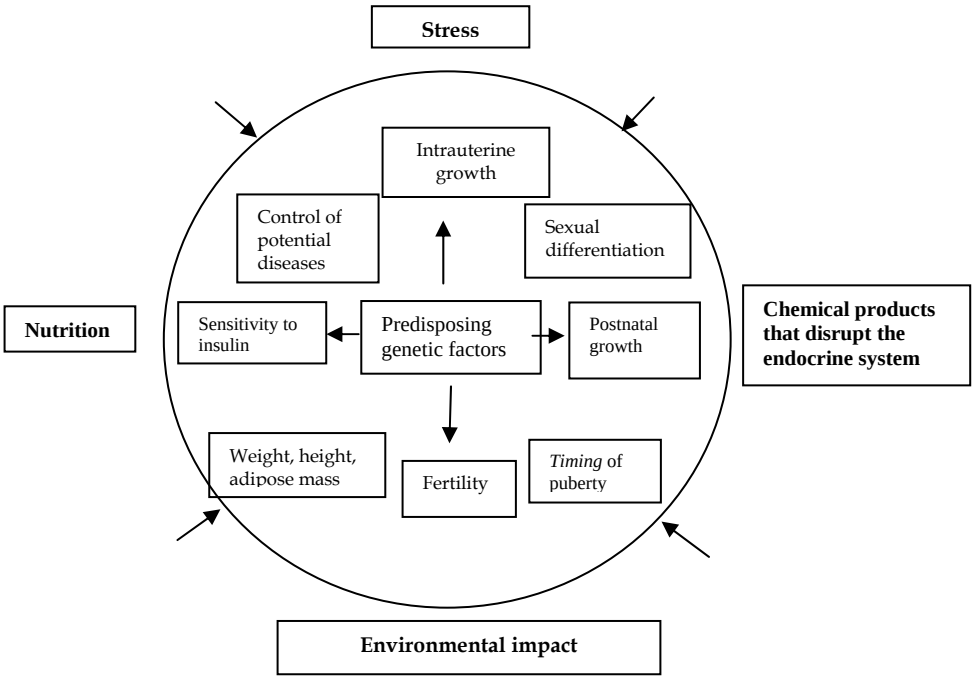
Other studies have focused on the secular trend of markers such as the development of breasts (girls) or genital organs (boys). In Sweden and Great Britain, breasts developed earlier in the 1980s than during the 60s and 70s. On the one hand, these findings highlight the existence of variations from one country to another and, on the other hand, show the importance of the marker used to assess the trend in the age of puberty (menarche and various stages in the Tanner classification system).

Epidemiological studies have attempted to isolate various factors correlated with variations in the age of puberty, essentially in girls. The average age of menarche in girls living in so-called "privileged" environments in the developing countries (Asia, Africa and South America) is comparable to that of girls from western countries in the Mediterranean Basin, but different from that of girls living in the same countries under less privileged conditions. This clearly highlights the influence of socio-economic conditions. Various studies have suggested a correlation between body weight and the age of onset of puberty. Girls with precocious puberty are more often obese than girls with delayed puberty, whereas the opposite applies to boys. A high body mass index from 36 months onwards is associated with precocious puberty in American girls.

Situations of physical and mental stress can delay puberty and this form of reversal in secular trend was actually observed during the war in Croatia and Bosnia. Conversely, other stressful situations can, however, trigger precocious puberty (immigration, adoption, *insecure* relationship with parents). The varying impact of the elements involved in a stressful situation suggests a heterogeneous neuroendocrine response to these different factors.

Numerous studies have focused on correlations between fetal and perinatal exposure to chemical products that disrupt the endocrine system (DDT pesticide) and precocious puberty. It is, however, difficult to isolate the chemical agents present in the environment in order to identify their respective effects on the endocrine system. Other factors mentioned (birth weight, exposure to light or climatic conditions, problems at school, etc.) would appear to warrant new studies.

Overall, the age of puberty is a complex physiological process, which is subject to a spectrum of intercorrelating factors.



Genetic and environmental factors influencing the age of puberty (according to Parent *et al.*, 2003)

Relationship between puberty and obesity

Numerous studies highlight the presence of a close correlation between adipose mass and puberty. The onset of puberty has long been known to depend on nutritional conditions and a deficient diet is linked with delayed puberty. Moreover, it appears that childhood obesity is constantly increasing in western countries accompanied by a lowering in the age of onset of puberty. A certain number of epidemiological studies indicate a highly probable correlation between the two phenomena.

Although a correlation between obesity and puberty seems to be well established, the causal relationship between excess weight and puberty has not been clearly defined. Studies have not been able to determine whether the pre-existence of excess weight is conducive to precocious puberty or, on the contrary, if hormonal changes accompanying puberty are responsible for the increase in adipose mass. In fact, some studies suggest that sexual maturity would be responsible, *via* an increase in sex steroids, for excessive weight gain in girls experiencing precocious puberty.

It should also be noted that most studies concerning correlations between obesity and puberty have been carried out in girls. This is probably due to the problems associated with evaluating sexual maturity in boys within the framework of epidemiological studies. Some studies carried out in boys show that the correlation between precocious maturity and obesity is completely reversed in boys compared to girls.

Finally, the discovery of leptin in 1994 shed new light on the correlations between adipose tissue, the hypothalamo-hypophyseal axis and puberty. Thus the 1998 finding focusing on obese patients with congenital leptin or leptin receptor deficiency showed that this hormone, which is produced by the adipose tissue, plays an extremely important role in the implementation of reproductive functions. Moreover, the administration of leptin for 18 months to a young adult male with leptin deficiency and immature until then, allowed full puberty to be induced, thus demonstrating that leptin plays a crucial permissive role.

However, obese children treated with leptin do not experience precocious puberty, which highlights the fact that the "leptin" signal alone is incapable of triggering puberty at a pre-puberty age.

Published data concerning the correlations between obesity and puberty clearly show the presence of a positive correlation between excess weight and early sexual maturation in girls. The difficulty in determining the direction of the correlation between excess weight and sexual maturation suggests that this is a two-directional correlation in which the accumulation of fat at the time of puberty could depend on the sex hormones (estrogen levels) but the quantity of accumulated fat could, itself, precipitate sexual maturation. In fact, adipose tissue could correspond to a secondary hormonal gland capable of influencing the synthesis and release of hormones such as estrogens, which would directly impact on sexual maturation. Finally, detection of the crucial role played by leptin, which is essential, but not sufficient, for normal sexual maturation in both girls and boys, emphasizes the importance of adipose tissue in triggering puberty.

Genetic aspects of growth

Heritability (h^2) is a quantitative statistical measurement, which can be used to estimate the contribution of the genetic component in a given trait. In other words, this data defines the respective role of genes and the environment at a given moment and in a given population. Generally speaking, the difficulty in studying a complex trait is compounded precisely by the difficulty in assessing its heritability. The precise characteristic aspects of the trait (phenotype) studied poses yet another problem. The very definition of the phenotype is, in fact, often uncertain for many complex traits. In the case of a quantitative trait, potential variations in the value measured in the same individual (or any error in measurement) contribute to an underestimation of the involvement of genetic factors.

Height, however, is one of the complex traits, which is easier to study. The measurement of height is extremely straightforward, reliable and accurate. It is a stable item of data over a long period in life. Height can, therefore, be routinely measured in large samples of a population without any difficulty and using few resources. At the level of the population, height during adulthood follows a normal distribution, suggesting the interaction of several factors.

Based on several clinical, physiological and pathological observations, it is a well-known fact that several genes are involved in determining the height of an individual. Numerous genes have, in fact, been associated with growth anomalies in man and it is therefore possible that polymorphisms (nucleotide variations) of some of these genes contribute to the height of individuals at the level of the population. The role of sex chromosomes in determining the average height is essential, as confirmed by the sexual dimorphism of height during growth or the abnormal height of patients presenting with gonosomal anomalies. The relevance of genetic factors is also indicated by the variability in the average height of individuals depending on their ethnic origin.

Other types of study have pinpointed the genetic component. According to adoption studies carried out in several countries (United States, Canada, Denmark, Sweden and Finland), intrafamilial correlations are stronger between children and their biological parents than between adopted individuals and their host family. The study of first cousins in numerous populations in the United States, France, Brazil and Norway, for instance, suggests a marked heritability. The first rigorously conducted study of twins was carried out in 1959 in a population of Swedish conscripts. It estimated height heritability at 0.60. Since then, other

studies conducted in the United States and Finland have detected higher heritability values (0.80). Moreover, recent heritability studies obtained from various genome screening programs carried out in order to identify potentially important genomic regions in determining height confirm these studies (heritability ranging from 0.69 to 0.95).

The comparison of cohorts of twins in 8 countries (Australia, Denmark, Finland, Italy, the Netherlands, Norway, Sweden and the United Kingdom) yielded interesting results on the variation in average height depending on the population. The highest values were recorded in the Netherlands (184 cm on average for men and 171 cm on average for women). The lowest values were recorded in Italy (177 cm on average for men and 163 cm on average for women). As the secular trend in increased height was similar in all these countries, the difference observed is probably linked to genetic factors. Heritability appears to be less marked in women. Environmental factors therefore seem to play a more significant role in determining height.

Numerous epidemiological studies have shown a marked association between height or birth weight and height during childhood and height during adolescence and adulthood. A study carried out in 40,000 young males highlighted an average difference of 7 cm between men with a birth weight below 2,500 g and those with a birth weight over 4,500 g. Similarly, the authors point out an average difference of almost 10 cm between men who measured 48 cm at birth and those who measured 55 cm. Another study carried out in twins shows that in pairs of dizygous and monozygous twins, the twin with the lower birth weight or height has the lower height during adulthood. Thus, a deviation of 1 kg in birth weight between dizygous twins is associated with a subsequent difference of 4.3 cm in height.

Three main approaches are used to identify the genetic variants that modulate height: the sequencing of candidate genes, association studies and link studies by genome screening.

Hundreds of syndromes listed in the OMIM[14] registry (Online Mendelian in Man) are associated with a very small stature. Some of these diseases are due to single gene mutations. Thus most cases of delayed growth of endocrine origin are linked to growth hormone deficiency (isolated or combined with other hypophyseal hormone deficiencies) or with a lack of activity. The few molecular mutations identified concern genes expressed along the somatotropic axis (growth hormone coding gene, its receptor, etc.) and an increasing number of transcription factors (HESX1, LHX3, LHX4, PROP1, POU1F1, SOX3 and SOX2, etc.) Other mutations of numerous genes involved in bone formation are responsible for skeletal dysplasia, which impacts upon height. The main genes responsible are *FGFR3* and *COL1A1*. Anomalies of the *SHOX* gene, located on the X chromosome, are probably more frequent. They are involved in subjects presenting with Turner syndrome as well as in patients diagnosed with a small idiopathic height.

Although data relating to the mutations responsible for severe growth anomalies are even more fragmented, they are essential in order to understand the physiopathology of several rare diseases, especially on an individual scale, so as to ensure improved management of patients and their families. These studies are also essential as a guideline for research, on the scale of an entire population, aimed at highlighting the most common molecular variants whose effects are much less important, and which can play a role in determining a complex trait such as height. Genes already involved in monogenic diseases can, in fact, be classed as potential candidates for analysis in order to attempt an explanation of variations in height in a given population.

[1] http:/www.ncbi.nim.nih.gov/omim

Most association studies are specifically based on the analysis of these candidate genes. Association studies on the full genome scale can, however, be increasingly envisaged given the advent of high-density DNA polymorphism cards and recent technological advances that allow genotyping at a high flow rate.

Association studies are typically based on a comparison of the frequency of certain alleles (at one locus or several loci) between a patient population and a control population. These studies are particularly interesting for detecting common variants with modest genetic effects. However, large samples are needed in order to highlight such effects, and these are seldom available. The results of these studies are rarely commented upon.

A correlation has been reported between common variants of around twelve genes and height: LH-β (*β Luteinizing hormone*); COLI A1 (*Collagen I A1*); VDR (*Vitamin D Receptor*); ESR1 (*Estrogen receptor*); DRD2 (*D2 Dopamine Receptor*); IGF-1 (*Insulin-like Growth Factor 1*); CYP17 (*Cytochrome P450c17a*); CYP19 (*Aromatase*); Y chromosome; PTHR1 (*PTH/PTHrP Receptor*); GH1 (*Growth Hormone 1*); PPARγ (*Peroxisome Proliferator-Activated Receptor-γ*). These variants have been investigated in genes presenting with severe mutations responsible for the afore-mentioned syndromes characterized by low height, and other genes deemed to be good candidates. Several of these genes have also been associated with another complex trait – the age of puberty, the heritability of which is also high.

Link studies have been widely used to identify numerous genes involved in Mendelian disease transmission. Such approaches are also interesting for analyzing a complex trait with strong heritability such as height. This trait has, therefore, been the subject of numerous studies. More specifically, one team reanalyzed the data of link studies by screening the full genome of four populations of adult individuals for whom both the genotype and height were available. The authors highlighted a link involving the following three chromosomal regions: 7q31.3-36, 12p11.2-q14 and 13q32-33. A fourth region, 6q24-25, yielded results close to the level of significance. Encouragingly, the data concerning chromosomes 6, 7 and 12 were pinpointed independently by other teams. Four other regions (9q22, Xq24, 6p21 and 2q21) were also highlighted and an epistasis correlation was detected between two of these loci (6p21 and 2q21), which would seem to influence adult height in the test sample.

Link and association studies are particularly promising approaches for identifying and characterizing the genetic component of a complex trait with marked heritability such as height. An understanding of the genetic foundations of growth anomalies remains a pre-requisite, not only for identifying genes, certain variants of which would seem to contribute to the variation in height on a population scale, but also in order to ensure a more effective management program for patients and their families.

Genetic aspects of the age of puberty

The normal age of onset of puberty lies within a gender-dependent range (8 to 13 years for girls and 9 to 14 years for boys). The latency period between birth and the onset of puberty corresponds to childhood in humans or the period of sexual immaturity in the rest of the animal kingdom. There is a close correlation between life span, gestation and the age of puberty in mammals, which suggests the interdependence of these three chronological factors. Childhood is a crucial period during which higher, cognitive functions reach neuronal maturity. Reactivation of the gonadotropic axis is also due to a process of neuronal maturation, the chronology of which is certainly determined during the life of the fetus or at birth.

Analysis of the genetic determinants of the age of puberty requires methodology that is difficult to implement. Puberty is a physiological process, the genetic determinism of which is certain although the relevance of environmental factors for mammalian reproduction is also recognized. The genetic determinism of the age of puberty has been demonstrated in several studies, the first of which date from 1929. A high mother-daughter correlation for the age of puberty is described in retrospective studies. These studies nevertheless raise the problem of analyses of an event that occurred several years earlier and which is sometimes poorly defined. There is a possible bias regarding age if the event is dated according to the calendar year of birth as opposed to the real age. Longitudinal studies have been carried out in order to eliminate any errors in retrospective assessment. They confirmed the marked genetic determinism of the age of puberty.

The second stumbling block with these correlation studies is the lack of specificity for the "menarche" variable to determine the age of puberty. Menarche attests to a process of complex, hormonal interactions, which depend on the endogenous production of steroid sex hormones, the sensitivity of peripheral tissues to these hormones and also "disruptive", exogenous factors having a steroid-like activity. This "pollution" by exogenous compounds also applies when assessing breast development. In addition to this phenomenon, obesity, which also affects the age of puberty in developed countries, is another factor that diminishes analytical reliability. Some studies have overcome this problem by assimilating puberty to a dynamic variable defined by a score, taking several pubertal development parameters into account. These studies have confirmed, even increased, the role of genetic factors in determining the age of puberty. Furthermore, this dynamic variable has restored the relevance of retrospective analyses.

The third point concerns the height of the study populations. This involves mega-analyses over several years, which demand a significant financial commitment and are thus often difficult to implement.

The definition of new biological constants in the initiation of puberty is an urgent requirement for investigating the role of genetic and environmental factors. Somatic changes occurring during puberty reflect deep-rooted hormonal changes. In many cases, it is difficult to distinguish between the cause and the consequence of the pubertal process. A growth peak known as the "pubertal growth peak" occurs during puberty, but the mechanisms are poorly defined. This peak is not entirely dependent on sex hormones. It is probably the reflection of the neuronal maturation of the somatotropic axis, which is partly dependent on that occurring on the gonadotropic axis. The genetic determinism of these biological variations during puberty has been modeled in a rather limited number of studies. This is a key point for a clearer definition of normal variations and for finding biological markers of the initial phases of puberty, or even the pre-puberty phase. These markers would be easier to analyze for epidemiological and health monitoring studies.

There is also a diagnostic interest in developing new markers for the onset of puberty. The analysis of delayed puberty attempts to distinguish between simple delayed puberty, without any subsequent repercussions on fertility, and permanent gonadotropic deficiency responsible for permanent infertility. This frequently accounts for consultations in pediatric endocrinology departments. There is currently no clinical or biological marker to predict changes towards normal puberty in a child presenting with isolated, delayed puberty. Only a molecular genetic analysis allows a conclusion to be made when a mutation is characterized.

The analysis of monogenic models of diseases affecting the onset of puberty is a strategy for ensuring a better understanding of the physiology of puberty. Puberty depends on the reactivation of the gonadotropic axis around 7–8 years of age. The absence of reactivation of the gonadotropic axis is responsible for delayed puberty or even the complete absence of

puberty and, consequently, infertility during adulthood. Conversely, accelerated activation is responsible for precocious puberty. Delayed puberty is often syndromic but isolated forms are also described. The latter provide an important source of information for clarifying the role of known proteins or for defining new proteins playing a major role in the onset of puberty. These studies of the genetic factors involved in isolated, delayed puberty do not account for the sporadic forms, which frequently occur.

Central, isolated, precocious puberty is a complex pathology, the genetic origin of which must be precisely modeled. Several arguments suggest a multifactorial genetic model. The description of factors promoting precocious puberty is absolutely essential for clarifying the physiological and physiopathological mechanisms of puberty.

Genetics can highlight elements influencing the long-term consequences of diseases affecting the onset of puberty. The gonadotropic axis is, in fact, the key element in reproduction. An analysis of the mechanisms involved in the onset of puberty describes new hormone systems, which are also important in adults. Several cancers are directly dependent on sex hormones. A correlation appears to exist between breast cancer and the age of puberty. This point raises several public health questions. Could the secular lowering of the age of puberty partly explain the increase in the prevalence of breast cancer in developed countries? Is there a link between predisposing genetic factors for advanced puberty and those conducive to the onset of a sex hormone-dependent cancer? Once again, the problem is centered on the description of new genetic or biological markers of the onset of puberty.

Neuroendocrine aspects of puberty and growth, and the role of leptin

It is now established that the onset of puberty is determined by events that take place in the brain and that the presence of gonads is not required for this process. This activation, which occurs at central level, leads to a synchronized increase in the pulsatile secretion of gonadoliberin or GnRH (*Gonadotropin Releasing Hormone*) by a handful of specialized neurons located in the hypothalamus. The secretion of GnRH stimulates the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones are then released into the general circulation and reach the gonads where they regulate their development and the secretion of gonad steroids. In return, these steroid hormones promote the growth of secondary sex hormones and trigger the onset of sexual dimorphisms (such as the distribution of fats, muscle mass, breast development, tone and voice).

In women, the first hormonal signs of puberty are detected at 8-10 years of age and manifest by the onset of a circadian rhythm of gonadotropin secretion (with higher LH levels during sleep). Menstruation first appears at the average age of 12 years with the first ovulation 6 to 12 months later.

It is increasingly evident that the trigger factor for puberty does not lie within the intrinsic ability of GnRH neurons to secrete their neurohormone in an episodic manner, but occurs as a result of the post-natal development of the brain, which leads to maturation of the networks of neurons and glial cells (non-neuronal cells in the nervous system, such as astrocytes), which are functionally related. It has long been known that GnRH neurons receive information from other neurons via synaptic contacts. Any change in the nature of these "external" signals such as a loss of trans-synaptic, inhibitory influxes on GnRH neurons could be the trigger factor in increasing GnRH secretion required for the onset of puberty. This "central brake" on puberty is fully functional during the juvenile postnatal development period, thus preventing a premature increase in GnRH secretion. An alternative but non-exclusive view suggests that pubertal activation of GnRH secretion is

triggered more so by an increase in excitation influxes, which are mainly transported by neurons using glutamate amino acid as the neurotransmitter. Recent studies show that, in addition to this neuronal control, glial cells and the growth factors that they produce play a fundamental role in this facilitatory process whereby the hypothalamus controls the secretion of GnRH during sexual development.

Are there routes of communication capable of coordinating neuronal and glial influxes facilitating the secretion of GnRH during the onset of puberty? Recent studies show that stimulating amino acids such as glutamate could be involved in this process. Thus, communication between the astrocytes and the neuronal networks that use the stimulating amino acids as a signaling mode could be a fundamental mechanism employed by the neuroendocrine brain to control the onset of puberty. The identification of new molecules involved in regulating communication between neurons and glial cells during the postnatal development period leading to puberty on the one hand, and the identification of genes controlling the pubertal clock on the other hand, will be a major channel of investigation in future years.

Recent studies suggest the role of leptin in growth and the onset of puberty. Initial observations showing that dietary restrictions delay the onset of puberty or alter the adult reproductive function have led to the hypothesis that individuals should reach a critical body mass and/or acquire a certain amount of adipose mass to facilitate the onset of puberty. From a biological standpoint, puberty represents a period in life during which rapid growth is associated with sexual maturation. Both these processes are most certainly regulated by peripheral metabolic factors, which inform the body of body height and adipose cell content. Even if, as was mentioned earlier, the signal initiating puberty remains unknown, the sequential link of major hormonal changes involving various systems such as leptin, and the activation of the gonatropic (involved in puberty) and somatropic (involved in growth) axes, could be the underlying cause.

Different studies carried out in animals have clarified this complex sequence of hormonal events. The administration of leptin, for instance, restores reproductive function deficiencies in genetically leptin-deficient mice (ob/ob: obese and infertile mice) and accelerates the sexual maturation and the onset of puberty in wild mice.

In man, circulating leptin levels gradually increase as pubertal maturation advances with, however, a clear-cut dimorphism between boys and girls. It is interesting to note that, in girls, a correlation exists between the onset of menarche and serum leptin levels: a threshold leptin concentration is required for the onset of menarche in girls. Leptin deficiency could thus be the primary cause of delayed puberty and menarche in undernourished children. The few cases of patients presenting with leptin deficiency or resistance, combined with mutation of the leptin gene or its receptor, show that this hormone is essential for the puberty process to function properly. In fact, female patients presenting with this deficiency also experience primary amenorrhea and no pubertal development whereas boys suffer from hypothalamic hypogonadism. Other studies, however, suggest that leptin would play a "permissive" as opposed to a "triggering" role in the process of sexual maturation. Leptin would, therefore, adopt a crucial role in the onset of puberty during postnatal development, allowing the maturation not only of metabolic projections but also of cells involved in controlling the reproductive function. All of these studies also suggest that any disruption in reaching the neonatal leptin peak could alter the establishment of hypothalamic circuits regulating food intake and the reproductive function.

The influence of early stress on puberty and growth

The ability of an organism to adapt to its environment is of vital importance and any changes in the ability of the organism to respond to stress-inducing agents, such as inadequate, excessive or prolonged responses may lead to "an allostatic charge" (cost inflicted upon the body to maintain stability) and to the onset of diseases. Although many people who are exposed to stress do not develop these diseases, stress appears to be a trigger factor in those who are particularly vulnerable, determined by genetic factors or early experiences.

Studies have focused on the role of adverse events on the neuroendocrine circuit of adaptive responses to stress and its long-term consequences on the principal endocrine axes involved in the growth and pubertal development of individuals.

Chronic hyperactivation of the hypothalamo-hypophyseal-adrenal axis (HPA or HHA, stress axis) can be determined by numerous genetic and environmental factors. The perinatal period, early childhood, childhood and adolescence are periods of increased plasticity of the stress-related system, and are consequently particularly sensitive to stress. In the early stages of life, the hormone system may have a structuring impact and long-term effects, which often persist throughout life. In adults, hypercortisolemia leads to the suppression of reproductive, thyroid, growth and immune functions.

Various prenatal stress animal models have been developed in order to clarify the mechanisms involved in the long-term effects of early experiences and to offset research difficulties encountered in humans in this particular field (longitudinal studies). These studies show that the hypothalamo-hypophyso-adrenal axis of the descendants is permanently affected by prenatal stress, which manifests in the form of various phenomena: prolonged secretion of corticosterone during exposure to stress in adulthood, the effects being more marked in women than in men, alterations in circadian rhythm and an increase in noradrenalin plasma levels indicating greater activation of the sympathetic nervous system.

Prenatal stress or early prenatal events not only impact upon the hypothalamo-hypophyseal-adrenal axis, but also on other endocrine factors such as sex hormones. In fact, prenatal stress during the critical period of hypothalamic differentiation has negative effects on testicular growth in the embryo and on future reproductive function. Prenatal stress alters the sexual behavior of males by suppressing the testosterone production peak during development, which is essential for masculinization of the brain and behavior.

Little is known about the effect of perinatal events on the growth factor axis. Maternal separation in rats increases the activity of the hypothalamo-hypophyseal-adrenal axis in the young and triggers hyposecretion of the growth hormone. The administration of growth hormone release factors cancels the suppression of growth hormone secretion induced by maternal separation in young rats.

The development of new animal models highlighting alterations in growth and sex differentiation by early environmental influences or genetic modifications should allow various hypotheses concerning the regulation of these important physiological factors to be tested. This strategy will help to clarify the question of individual differences in relation to the impact of stress on growth and reproductive function, and to elucidate the mechanisms that link stress to changes in growth and reproduction. An important avenue for future research is to determine the mechanisms by which early stress triggers a long-term effect.

Recommendations

Various studies have shown a secular trend with faster growth and development, greater average heights and earlier maturation. Most of this secular trend in adult height is reached as from 2 years of age. Accelerated growth shortens the overall growth period. Thus, nowadays, peak pubertal growth occurs at a younger age and adult height is reached earlier.

Improved understanding of the links between the onset of puberty, environmental factors and the onset of diseases affecting growth and/or sexual maturation warrants the implementation of large-scale, longitudinal, epidemiological studies comprising a clinical, biological and genetic approach.

The development of new models for studying anomalies in growth patterns and sexual differentiation (particularly animal models that have been genetically modified and/or exposed to various environmental factors at different stages in development) should allow several hypotheses concerning the regulation of these important physiological functions to be tested.

French research lacks coordinated projects on growth, puberty, nutrition and the correlation between these phenomena. These network studies, however, could improve our understanding of the mechanisms involved in these physiological and pathological processes, and could have significant consequences for public health. Such topics could, for instance, be incorporated in an ANR program entitled, "Post-natal development: genetic and environmental determinants" and integrate the following research recommendations.

DEVELOP A FRENCH POPULATION HEIGHT AND WEIGHT STUDY

France does not have any recent reference material concerning representative, transversal or longitudinal population data. It is, however, generally admitted that the changes observed in growth and development are good indicators of the living conditions of a society and, in particular, of the nutritional and health status of a population. Following growth parameters over time can highlight a population's state of health and, at the same time, any health-related discrepancies within the same population. Regular measurements of the growth status of a population are still important as these constitute an appreciable resource for evaluating public health.

The expert group recommends that this tool be developed in France, at least in terms of height and weight, but geographical variations and family origin should also be borne in mind.

Two types of study are available: a transversal study, which establishes the missing reference data in France and a longitudinal study to refine these references, which can be combined with biological, physiological and genetic data and with new markers to be determined.

INVESTIGATE BIOLOGICAL MARKERS OF THE EARLY PHASES OF PUBERTY

The indicators of the normal onset of puberty are still inadequately defined, even today. This situation has a deleterious effect on the management of pubertal anomalies. The expert group recommends an investigation into biological markers that would be reliable indicators

of the onset of puberty in both sexes. These indicators could be used within the framework of epidemiological studies to investigate the interactions between growth, puberty and the environment. They could also be used in the management of patients affected by a puberty-related disorder.

DEVELOP STUDIES TO ESTABLISH THE DYNAMIC MECHANISM BEHIND PUBERTY AND ITS CONSEQUENCES

Studies that take into account the dynamic mechanism behind puberty would provide an opportunity for defining a score, which could easily be used in community practice.

The expert group recommends that a study on trends in the age of puberty be carried out in France in relation to changes in the environment (nutrition, exposure to endocrine disturbances and lifestyle, etc.). A substantial effort must be made to evaluate potentially disruptive endocrine factors. The expert group advocates the specific study of the link between endocrine disturbances, the age of puberty and the onset of hormone-dependent cancers.

An increase in the prevalence of obesity in western countries and advances in the age of puberty raise the question of the correlation between these two phenomena. In fact, despite the correlation highlighted between obesity and precocious puberty in females, the causal relationship and the direction of this correlation have yet to be elucidated. This question has yet to be answered in man. It should be remembered that this problem is linked to the absence of reliable markers of the onset of puberty. The expert group recommends that research be continued in this field (using carefully selected animal models in particular).

IMPROVE KNOWLEDGE OF THE GENETIC FACTORS INVOLVED IN THE ONSET OF PUBERTY

Puberty is a physiological process. Very few genes contributing to the onset of puberty have so far been identified. An analysis of the genetic determinism of the age of puberty requires a methodology that is difficult to implement. Puberty studies can extend our knowledge of the regulation and reproduction mechanisms in adulthood.

The expert group recommends the consideration of a large-scale study allowing the genetic determinism of the age of puberty to be modeled and the genetic factors involved to be identified. These studies could provide information on the link between the age of puberty, environmental factors and hormone-dependent cancers. This line of investigation could also open up new avenues for treatment.

IMPROVE KNOWLEDGE OF THE GENETIC FEATURES OF GROWTH ANOMALIES

Knowledge of the genetics of a complex trait such as individual growth (height) is still highly fragmented whereas various studies, including those carried out in twins, clearly show the importance of genetic factors. The interactions between environmental and genetic factors warrant further investigation. Furthermore, the links between the dynamic mechanism behind growth and cancer have not been fully explored to date.

The expert group recommends that studies aimed at identifying the key genes involved in growth-related disorders be continued. As we have already seen, the identification of these genes may have considerable clinical implications (not only in terms of diagnosis but also as regards prognosis and treatment). However, based on current knowledge, few patients are directly affected by this progress, which, furthermore, helps to promote understanding of the physiology of growth. At the same time and taking diagnostic and therapeutic implications into account, it is important to encourage research aimed at identifying new growth hormone (GH) secretion markers. The relevance of numerous tests used both in France and abroad, and based essentially on an evaluation of circulating levels of GH under various pharmacological stimulations, is, in fact, extremely debatable.

IMPROVE KNOWLEDGE OF POSTNATAL NEUROENDOCRINE MATURATION

Activation of the gonadotropic (involved in puberty) and somatotropic (involved in growth) axes after birth is due to a neuroendocrine maturation process that has not been clearly elucidated. These mechanisms appear to be highly dependent on the postnatal environment. For instance, the importance of the nutritional environment is emphasized in studies showing that, during a critical time frame, leptin plays an organizing function at central level. The effects of the postnatal environment deserve to be investigated from both an experimental and epidemiological viewpoint using appropriate markers.

Studies have focused on the role of adverse events on the neuroendocrine circuit of responses in relation to stress and its long-term consequences on the main endocrine axes involved in the growth and pubertal development of individuals. Chronic hyperactivation of the hypothalamo-hypophyseal-adrenal axis may be determined by numerous genetic and environmental factors. The perinatal period, early childhood, childhood and adolescence are periods of increased plasticity of the stress-related system, and are consequently particularly sensitive to stress. In the early stages of life, the hormone system may have a structuring impact and long-term effects, which often persist throughout life. In adults, hypercortisolemia leads to the suppression of reproductive, thyroid, growth and immune functions. The effect of stress on neurogenesis can also be investigated in experimental studies.

Appendix

Inserm collective expert review

Methodology

An Inserm collective expert review[2] sheds scientific light on a given subject in the field of health on the basis of a critical analysis and synthesis of the international scientific literature. The expert reviews are implemented at the request of institutions wishing for access to recent research data pertinent to their decision-making process with respect to public policy. An Inserm collective expert review is to be considered as an initial stage that is necessary but most frequently not sufficient to result in decision-making. The conclusions of the collective expert review contribute to, but cannot replace, debate between the professionals involved or society debate if the questions addressed are particularly complex and sensitive.

At the request of an institution, the Inserm collective expert review may be accompanied by an 'operational' expert review addressing application of the knowledge and recommendations and taking into account contextual factors (existing programs, structures, players, training, etc.). The latter type of expert review elicits contributions from the players in the field able to respond to the feasibility aspects, representatives of the administrations or institutions responsible for promoting applications in the field involved, experts having contributed to the reviews, and representatives of patient associations. The sharing of varied cultures and experience enables a complementary approach to the collective expert review in an operational framework. Moreover, a variety of work (recommendations for good practices, public hearings, etc.) implemented under the auspices of the High Authority for Health (HAS) may follow an Inserm collective expert review.

Collective expert review has been an Inserm mission since 1994. Some sixty collective expert reviews have been implemented in numerous health fields. The Institute guarantees the conditions under which the expert review is implemented (exhaustiveness of the document sources, qualification and independence of the experts, transparency of the process).

The Inserm Center for Collective Expert Reviews organizes the various stages of collective expert review from the initial problem statement through to communication of the report, with the assistance of Inserm departments. The Center team, consisting of engineers, researchers and a secretariat, implements the document searches, logistics and chairing of the expert review meetings. The team contributes to the scientific writing and to compiling the expert review products. Regular exchanges with other public organizations (EPST) implementing the same type of collective expert review have enabled similar procedures to be set up.

Problem statement

The problem statement phase enables definition of the institution's request, checking that accessible scientific literature on the issue raised is available and drawing up specifications which state the framework of the expert review (status report on the perimeter and main themes of the subject), its duration and budget, documented by a convention signed by the sponsor and Inserm.

During the problem statement phase, Inserm also organizes meetings with patient associations in order to ascertain the questions those associations wish to have addressed and the data sources available to them. The information is incorporated in the scientific program of the expert review. For certain subjects, exchanges with industrial partners are indispensable in order to obtain access to complementary data not available in the databases.

[2] Inserm accredited label

Expert review monitoring committee and assistance unit setup

A monitoring committee consisting of the institution and Inserm representatives is set up. The committee meets several times during the expert review to monitor the progress of the review, discuss any difficulties encountered in addressing the issues, ensure compliance with the specifications and examine any new factors in the regulatory and political context pertinent to the ongoing review. The committee also meets at the end of the expert review for presentation of the conclusions and prior to compilation of the final version of the report.

For expert reviews addressing sensitive issues, an assistance unit is also set up and consists in representatives of the Directorate General of Inserm, scientific board, ethical committee of Inserm, communication department, human and social science researchers and specialists in the history of science. The role of that unit is to identify, at the start of the expert review, the issues liable to have strong resonance for the professionals involved and civil society, and to suggest hearings of professionals in related fields, representatives of civil society and patient associations. In short, the unit is responsible for measuring the perception that the various recipients may have of the expert review. Before publication of the expert review report, the assistance unit pays special attention to the wording of the synthesis and recommendations, including, if necessary, the expression of the various points of view. Downstream of the expert review, the unit is responsible for strengthening and enhancing the circulation of the results of the expert review, for instance by holding colloquia or seminars with the professionals of the field and players involved or holding public debates with representatives of civil society. Those exchanges are to ensure enhanced understanding and adoption of the knowledge generated by the expert review.

Literature searching

The specifications drawn up with the institution are translated into an exhaustive list of scientific questions reflecting the perimeter of the expert review with the assistance of referral scientists in the field and members of Inserm. The scientific questions enable identification of the disciplines involved and construction of a key-word arborescence employed in the systematic searching of international biomedical databases. The articles and documents selected on the basis of their pertinence with respect to answering the scientific questions constitute the document base, which is forwarded to the experts. Each member of the group is asked to add to the document base over the course of the expert review.

Institutional reports (parliamentary, European, international, etc.), raw statistical data, associations' publications and other documents from the gray literature are also inventoried (non-exhaustive) in order to complement the academic publications provided to the experts. The experts are responsible for taking or not taking into account those sources depending on the interest and the quality of the information supplied. Lastly, a review of the main articles in the French press is supplied to the experts during the expert review in order to enable them to follow developments on the theme and the social repercussions.

Constitution of the expert group

The expert group is formed on the basis of the scientific skills necessary for analysis of the bibliography collected and on the basis of the complementarity of the group members' approaches. Since an Inserm collective expert review is defined as a critical analysis of the academic knowledge available, the choice of the experts is based on their scientific skills certified by publications in peer-review journals and their recognition by their peers. The expert recruitment logic, based on scientific skills and not on knowledge in the field, is to be stressed in that it is a frequent source of misunderstandings when the expert reviews are published.

The experts are selected from the French and international scientific community. They are to be independent of the partner sponsoring the expert review and recognized pressure groups. The composition of the expert group is validated by the Directorate General of Inserm.

Several scientists outside of the group may be requested to contribute occasionally to a particular theme during the expert review.

Expert review implementation lasts between 12 and 18 months, depending on the volume of literature to be reviewed and analyzed and the complexity of the subject.

Initial expert group meeting

Before the first meeting, the experts receive a document explaining their mission, the scientific program (issues to be addressed), schedule, the expert review bibliographic database to date and articles more specifically addressing certain experts on the basis of the skills.

During the first meeting, the expert group discusses the list of issues to be reviewed and completes or modifies it. The group also examines the document base and proposes supplementary searches with a view to enriching that base.

Expert critical analysis of the literature

During the meetings, each expert orally presents a critical analysis of the literature with respect to the aspect allocated to the expert in his/her field of expertise and communicates the accepted facts, uncertainties and controversies with respect to current knowledge. The questions, remarks and points of convergence or divergence elicited by the group analysis are taken into consideration in the section that each of the experts compiles. The analysis report, consisting of various sections, thus constitutes the state of the art for the various disciplines pertinent to the issue under review. The bibliographic references used by the expert are cited in and at the end of each section.

Synthesis and recommendations

The synthesis summarizes the broad lines of the literature analysis and identifies the main findings and principles. Contributions from contributors outside the group may be summarized in the synthesis.

The synthesis is more specifically intended for the institution and decision-makers with a view to use of the knowledge presented therein. The wording of the synthesis is to take into account the fact that it will be read by non-scientists.

As of report publication, the synthesis is posted on Inserm's website. The synthesis is translated into English and posted on the NCBI/NLM site (National Center for Biotechnology Information of the National Library of Medicine) and Sinapse site (Scientific INformAtion for Policy Support in Europe, European Commission site).

If requested by the institution, certain collective expert reviews include 'recommendations'. Two types of 'recommendations' are formulated by the experts group. 'Principles for action' based on a validated scientific reference system with a view to defining future public health action (mainly in screening, prevention and management) but which are not under any circumstances to be considered 'operational' recommendations insofar as no economic or political components have been taken into account in the scientific analysis. 'Research orientations' are also proposed by the experts group with a view to filling in the gaps in scientific knowledge observed during the analysis. Once again, these proposals cannot be considered 'priority' research without their being put into perspective. That is the task of the pertinent authorities.

Critical review of the report and synthesis by prominent 'readers'

For certain expert reviews addressing sensitive subjects, a critical reading memorandum is requested from several prominent 'readers' selected on the basis of the scientific or medical knowledge and managing or evaluating French or European research programs or having contributed to ministerial working groups. Similarly, the report and synthesis (and recommendations) may be submitted to figures with good knowledge of the 'field' and able to grasp the socioeconomic and political issues associated with the knowledge (and proposals) presented in the expert review.

Presentation of the conclusions of the expert review and debate

A seminar open to the various sectors involved in the subject of the expert review (patient associations, professional associations, unions, institutions, etc.) enables an initial debate on the conclusions of the expert review. On the basis of that exchange, the final version of the synthesis document incorporating the various viewpoints expressed is compiled.