CHAPTER 10

Environmental Effects on Growth

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Contents

10.1 Introduction 245
10.1.1 Research Design Issues 246
10.2 Temperature and Climate 247
10.3 Season 249
10.4 High-Altitude Hypoxia 250
10.4.1 Prenatal and Early Postnatal Adaptation 251
10.4.2 Childhood and Adolescence 253
10.4.3 Changes in Shape and Proportion 255
10.4.4 Molecular Control of Adaptation and Growth 256
10.5 Sleep 258
10.6 Pollutants 260
10.6.1 Cigarette Smoking 262
10.6.2 Air Pollution 265
10.6.3 Organic Compounds 265
10.6.4 Lead 268
10.6.5 Radiation 270
10.6.6 Noise Stress 271
10.7 How Do We Interpret Differences in Growth Related to Environmental Factors? 273
10.8 Conclusion 274
References 274
Suggested Reading 285
Internet Resources 286

10.1 INTRODUCTION

A chief characteristic of human growth and development is that it is "eco-sensitive"; it is sensitive to a wide variety of features of the environment. Among the most often studied are features of the natural environment, and usually these are studied as extremes (extreme cold or heat, aridity, high altitude). To these we must add anthropogenic features such as air pollution, metals (mercury, lead), pesticides and herbicides such as DDT, and energy (radiation and noise). Most anthropogenic factors are recent

N. Cameron & B. Bogin (eds): Human Growth and Development, Second edition.
ISBN 978-0-12-383882-7, Doi: 10.1016/B978-0-12-383882-7.00010-6

developments, and may pose adaptive challenges that are reflected in altered patterns of growth.

The study of human growth in relation to the natural environment has been one of the fundamental research areas in the study of human variation and adaptation.[1] By the mid-twentieth century, patterns of growth that were responses to environmental extremes, including slower maturation and reduced growth, were interpreted as adaptations, that is, relatively beneficial to the individual by providing some benefit in terms of function, survival and/or reproduction. While these benefits have rarely been measured, the theory that growth is a way for individuals to adapt to their immediate physical environment has been around since the 1960s.[2] Thus, the idea that growth responses are part of the adaptive potentialities of *Homo sapiens* is found in virtually all texts on human biological adaptation.[3–5]

Another interpretation of reduced growth and slowed maturation is that it is a direct result of adverse circumstances. James Tanner, who led the field of human growth and development for decades, noted the relationship between adverse circumstances in childhood and poor growth.[6] He championed the use of child growth as an index of community well-being, of health, and even of the moral status of a society as inequality of growth among different social groups reflected the unequal distribution of health resources. He called this study auxological epidemiology. In this view, slow or less growth indicates poorer health and the lack of adaptation in the face of nutritional or social disadvantage and adversity. Thus, researchers use two general and somewhat contradictory interpretations of environmentally influenced growth patterns (see Bailey and Schell for a review and discussion of the applications of these interpretations).[7]

This chapter focuses on environmental influences on growth including aspects of the natural environment and anthropogenic factors. Because of this dual focus, the contradictory interpretations of growth will be considered after a review of the relevant data on growth and the environment.

10.1.1 Research Design Issues

Studies of growth patterns in relation to environmental factors demonstrate several issues in the design of growth studies. Foremost of these is the issue of balanced precision, the idea that the independent variable (the "cause") and the dependent variable (the "effect") should be measured with equal precision. The earliest growth studies examined size (the dependent variable) in relation to age (the independent variable). Today, studies of growth and the environment require accurate and reliable measurements of both individual growth and the environmental factors, but this is not always achieved. Measuring the environment is straightforward when the environmental factor is not modified by behavior or culture and everyone living in one community has basically the same exposure throughout their lives (e.g. high-altitude studies). However, it is more difficult to measure pollutant exposures because individuals in a single community can vary greatly in level of

exposure. Some pollutants leave long-term residues in the body that can be measured retrospectively to estimate past exposure, for example lead measured in blood and bone, while others leave little trace of past exposure. Exposure to energy, such as radiation or noise, does not leave a residue at all and this makes retrospective studies very difficult. This fact explains much of the difficulty in determining the effects of mobile phones that emanate microwave radiation, since past radiation exposure is extremely difficult to reconstruct. At present, the study of environmental influences on growth is limited by our ability to measure environmental factors, and the information reviewed below should be understood as a limited picture wrested from substantial difficulties measuring the environmental factors of greatest concern to human well-being.

10.2 TEMPERATURE AND CLIMATE

Climate appears to influence growth and development, helping to determine body size and proportions. According to Bergmann's and Allen's rules, body size and proportions of warm-blooded, polytypic animals are related to temperature. In humans, Allen's rule predicts longer extremities and appendages relative to body size in warmer climates, and shorter ones in colder climates. Bergmann's rule predicts larger body sizes in colder versus warmer climates.

There is ample statistical evidence for a relationship between adult size and shape consonant with Bergmann's and Allen's rules. Roberts[8] examined published data on body dimensions of multiple samples of males from around the world and correlated the sample means with measures of local temperature. There is a significant negative correlation between body weight and mean annual temperature, as well as a negative relationship between sitting height as a proportion of total height and temperature (Figure 10.1). Newman[9] tested Bergmann's and Allen's rules through examination of aboriginal males in North and South America spanning 1000 years: smaller statures are observed near the equator consonant with Bergmann's rule, while the shorter legs among the Inuit are consonant with Allen's rule. In addition, the amount of body surface area tends to increase from cold to hot climates.[10] An analysis of samples measured since Roberts' landmark paper of 1953 showed that temperature was still related to body size, weight to height proportions and height to torso proportions, although the relationships were weaker than in Roberts' analysis. The effect moderation was due to greater weight among samples from more tropical regions, which could well be due to a nutritional transition in these lands.[11] The combined effect of nutrition and temperature demonstrates how phenotypic development is the product of multiple environmental influences.

The relationships observed between body proportion and environmental temperature can be explained in terms of the body's thermoregulatory process. In hot, dry environments, a body that has greater surface area relative to total body size or volume will more efficiently dissipate heat produced by the body's metabolism and activity.

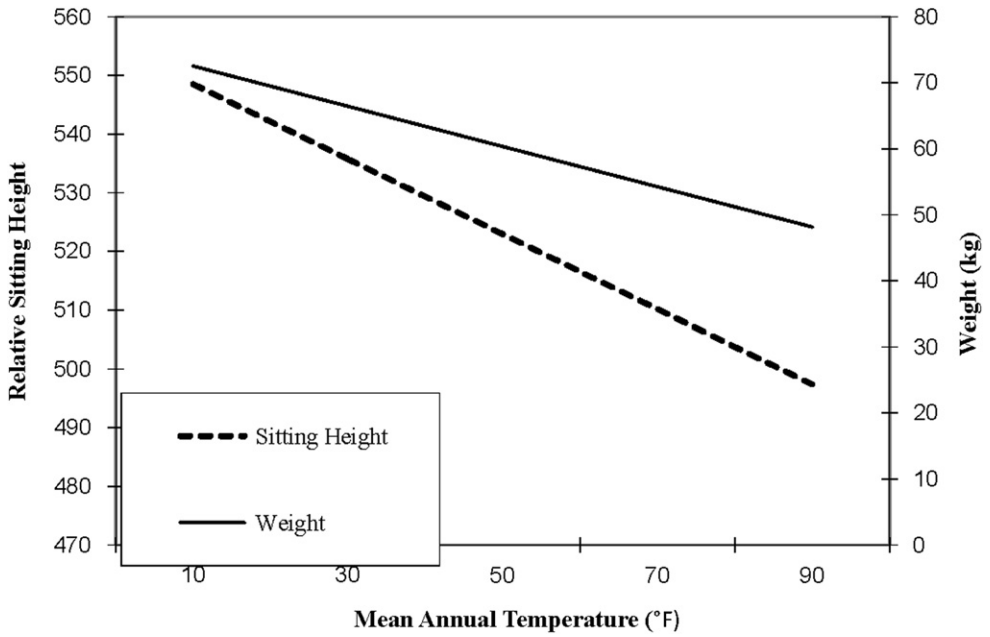

Figure 10.1 Relationship between mean annual temperature and body weight. *(*Source: *Adapted from Roberts.*[8]*)*

The reverse is true for cold environments where heat retention is important to avoid hypothermia; thus less surface area through which heat would be lost is more adaptive. The small stature and low body mass of populations in tropical rainforests, for example the pygmies in Africa, is an adaptive body shape because the high humidity in these environments limits the effectiveness of sweating, which dissipates heat through evaporation. The smaller body mass of these populations minimizes heat retention.[10]

The focus on the effects of temperature has primarily been on adult form, and only a few studies have examined the relationships of growth parameters to temperature. Malina and Bouchard[12] suggest that the typical body shapes associated with extremes in temperature have implications for development. For example, studies of the mean age at menarche demonstrate a negative correlation with annual mean temperature, indicating earlier maturation among females in hotter climates.[8,12]

Eveleth[13] conducted a longitudinal study of well-off, well-nourished American children in Brazil to determine the effects of the hot climate on growth. She observed that the Rio children weighed less than well-nourished, middle-class US children from Iowa, and had less weight for height, indicating a more linear body form in Brazil. Limb growth also was more linear and less stocky, with more surface area to volume. This growth of size and shape is consistent with expectations from Bergmann's and Allen's rules. Age at menarche, however, did not differ between the Brazilian and US populations, indicating that the populations were maturing at similar rates.

In humans, there appears to be a general relationship between climate and body size that roughly adheres to Bergmann's and Allen's rules. How this relationship develops through growth patterns has not been intensively studied and is not well understood.

10.3 SEASON

Seasonal variation in growth rates has been observed in healthy children. A classic study by Palmer[14] showed that growth rates for height are greater during the spring and summer months, while rates of weight gain are greater during the fall (autumn) and winter. The greatest increases in weight are often in September to November, and can be up to five times the weight gain in the minimal months from March to May.[15] Approximately two-thirds of the annual weight gain occurs between September and February. This seasonal rhythm in weight gain is not established in children until about 2 years of age. These observations were based on a temperate latitude population living in the northern hemisphere.

Height growth, on the other hand, reaches its maximum from March to May in the northern hemisphere. The average velocity is two to two-and-a-half times the average velocity during September to November, the period of minimal height growth.[15] Finally, one study has suggested that minimum weight gains and maximum height gains occur simultaneously.[16] It is worth noting that these are seasonal trends in the average growth velocities. Individual patterns of growth do not necessarily conform to these seasonal peaks in growth; in fact, the timing of individual peaks in growth can vary significantly.[15]

Seasonal variation in growth is not limited to temperate zones, and variation in growth rates between dry and rainy seasons has been observed in tropical climates. In Guatemala City male and female preadolescent and male postadolescent children follow a seasonal pattern, but adolescent children do not.[17] The absence of an effect during adolescence may be due to the pubertal growth spurt, which is quite large and its occurrence is highly variable between individuals.

A possible explanation for all seasonal variation in growth in height may be variation in sunlight, which influences the hormones involved in growth regulation.[10] Swedish boys exposed to sunlamps during the winter averaged 1.5 cm more growth in height than unexposed controls (Nylin, 1929, cited in Refs 10 and 15). However, during the summer, the control group grew more rapidly than the exposed boys, resulting in no overall difference in mean annual growth in height. Among blind children, the months of maximal growth were evenly distributed throughout the year while for normally sighted children the months of maximal growth occurred between January and June.[18] The seasonal variation in day length was posited as an explanation for the consolidation of maximal growth into the 6 months for children with normal vision. A test of this hypothesis examined growth rates of children living on the Orkney Islands, where there

is very large seasonal variation in day length. Growth was poorly correlated with climatic variables, suggesting that day length is the critical variable.[19]

What is critical, day length or sunlight exposure? A study of children in Zaire, Africa,[20] found that the growth in height was more rapid during the dry season than during the rainy season. Even though length of day was longer in the rainy season, actual exposure to bright sunlight was greater for the children during the dry season, supporting the role of sunlight in growth regulation.[10] The study by Bogin[17] of children in Guatemala also demonstrated that children aged 5—7 years grew more rapidly during the dry than the rainy season, and similarly to the African sample, exposure to sunlight was greater during the dry season.

Exposure to sunlight has long been recognized as an important factor for skeletal development. Ultraviolet light stimulates the production of cholecalciferol, vitamin D_3, in human skin, and vitamin D_3 increases intestinal absorption of calcium and regulates the rate of skeletal remodeling and mineralization of new bone tissue.[21] Despite the fortification of milk in some countries with vitamin D_2, the major source of vitamin D for humans is the body's synthesis of the D_3 form under stimulation from sunlight.[22] In addition, the marked seasonal variation of vitamin D derivatives in plasma coincide with variation in sunlight.[23] Thus, exposure to sunlight and the production of vitamin D_3 may account for the observation that children in temperate climates have a faster rate of growth in height during the spring and summer, and that children in the tropics grow more during the dry season, when sunlight exposure is greatest.

The seasonal variation of weight gain can be explained in some populations by seasonal differences in resource availability, nutritional variation and rates of disease, but for other, more well-nourished populations this explanation is not sufficient and there may exist an endogenous seasonal rhythm of weight gain in children.[10] Further studies are required to better understand this phenomenon.

There appears also to be seasonal variation in menarche, with higher incidences of menarche in spring and summer possibly due to variation in light, nutrition and/or disease.[24]

10.4 HIGH-ALTITUDE HYPOXIA

As we climb above 3000 m (about 10,000 feet), environments present reduced biomass, aridity, shortened growing seasons, diurnal cold stress, high solar radiant energy loads and reduced oxygen availability. Because this last challenge, called hypoxia, cannot be ameliorated by culture or technology, it should allow us a window on growth responses to a single, uniquely constant environmental stressor. In practice, however, the view is obscured. Growth outcomes at altitude are a cumulative history of myriad adaptive successes or failures. Not all moments in that history have equal impact. Our physiological adaptations are themselves mediated by genes facing natural selection. Pathways

between those genes and growth outcomes are poorly mapped. Lastly, growth responses of the approximately 140 million people who live worldwide at high altitude are constrained by disparate gene pools filtered through differing histories of occupation. The windows may not be comparable.

Altitude's effects on growth begin with how cells respond to hypoxia. Normal cells require partial oxygen pressures (PO_2) averaging about 23 mm in the cytoplasm, which dips below 5 mm in the mitochondria.[25,26] Since rates of oxygen exchange are determined by simple diffusion, cells face inevitable stress as we climb and the gradient between atmospheric and cellular oxygen declines. At sea level, the difference is 136 mm. At 4572 m (15,000 feet), this gradient is halved. Moreover, because of reduced carbon dioxide at high altitude, initial respiratory alkalosis also compromises hemoglobin's release of oxygen. Cellular effects of reduced PO_2 in tissue can be detected as low as at 600 m (1968 feet), but become clinically obvious by 3000 m (9842 feet).[25,27,28] At this point, cells begin to trade growth metabolism for maintenance of oxygen tension. Our bodies respond to these local trade-offs through physiological adaptations. Over time, cardiovascular and respiratory morphology also change.[25,26] Growth thus can be seen as a snapshot of how successfully these adaptations buffer our cells from hypoxia.

Adaptation has its limits, however. The highest permanent settlements are La Rinconada in Peru and Ma Gu in Tibet, both at roughly 5050 m (16,570 feet).[29] When the gradient between capillary and cell PO_2 disappears altogether, at approximately 9000 m (29,528 feet), cellular metabolism fails and death ensues.[25,26] Not surprisingly, then, occupation of high-altitude regions has been comparatively recent. While the Tibetan Plateau may have been sporadically exploited since 25,000 BP, and the Andean altiplano for half that long, sustained settlement occurred only about 6000 and 3000 BP, respectively, while the Ethiopian Semien highlands were occupied after 6000 BP.[30]

10.4.1 Prenatal and Early Postnatal Adaptation

The most dramatic effects of hypoxia on growth occur before birth. Placentas of indigenous Andean women at high altitude are up to 15% heavier relative to birth weight, and have three times more non-symmetrical shapes; both changes enhance surface area for oxygen transport.[29,31–33] Some studies show increased rates of blood flow in placental tissue of indigenous women[34–37] associated with higher birth weights. Flow rates in Tibetans are associated with markedly higher levels of nitric oxide (NO) metabolites, which are powerful vasodilators.[36,38] Bolivian Aymara show lower NO expression than Tibetans at comparable altitudes, but higher than lowlanders initially exposed to hypoxia. However, different flow rates or oxygen saturations were not found to influence net oxygen delivery to fetuses of Aymara or European ancestry.[37] In this context, early tissue growth, particularly skeletogenesis, is already mildly hypoxic, with well-described molecular compensations.[39] At high altitude, theory predicts that such existing pathways will be utilized for adaptation.

Hypoxia also drives changes in fetal size and body proportions. Ultrasound measurements of second trimester fetuses deprived of oxygen due to maternal smoking or diabetes showed reduced lower limb growth, changes in head shape and reduced length.[40,41] Models of fetal development have been developed that variously emphasize maternal oxygen transport, metabolic control mechanisms in the placenta or trade-offs between oxygen tension and glucose utilization.[32,34,37,42–46]

At birth, reductions of 50–100 g per 1000 m of altitude are the rule. Lean tissue comprises most of the loss.[31,32,42,47,48] Interpopulation variance can be pronounced. Neonates of Han immigrants in Lhasa, for instance, had mean birth weights over 800 g lower than normal-term sea-level white neonates in the USA, and about 250–300 g below European or Aymara Bolivians, while Tibetan neonates in Lhasa ranged from 450 g below the US norms to slightly above.[35]

Such disparate outcomes to a single constant stress may reflect different adaptive mechanisms. Higher Tibetan birth weight, compared to Peruvian Indians or residents of Leadville, Colorado (3026 m), were significantly correlated only with increased maternal uterine artery flow rates during pregnancy, while Peruvian and Leadville birth weights correlated only with maternal blood oxygen saturation.[42]

Significantly, the roughly normal distribution of birth weights characteristic of sea level shifts left at high altitude. Low birth weight (LBW) can become up to four times more prevalent, approaching half of all births. Thus, while mean change between sea level and high-altitude birth weight may have minor clinical significance, the left shift of the new distribution, already populated by children at or near risk of LBW, will extend many more neonates into high-risk categories.[48]

Peruvian neonates at high altitude also demonstrated reduced muscle mass relative to sea-level controls, but similar levels of body fat.[49] This could indicate gestational constraints, or prenatal adaptation to energy or oxidative stress through reduction of actively metabolizing lean tissue and associated mitochondria. For the latter reason, optimal birth weight at high altitude has been estimated to be 170 g lower than at sea level.[28]

Parental ancestry influences birth outcomes at altitude. Despite their socioeconomic advantages, one-third of all neonates of pure European ancestry in La Paz, Bolivia, were small for gestational age (SGA), compared to 16% of lower socioeconomic status Mestizo neonates and 13% of pure indigenous Aymara mothers.[34,35] Unlike lowland populations, maternal weight, parity or level of prenatal care were not significant predictors of birth weight, suggesting that hypoxic stress is the limiting factor. Birth weight response also may be associated with the sex of the parent of high-altitude ancestry. Controlled for gestational age, European fathers contributed more to birth weight increases than mothers. The effect, consistent with parental competition over epigenetic imprinting, dropped out when both parents were Aymara. The selective impact of hypoxia thus can override mechanisms that operate at sea level.[50]

In sum, the period from second trimester to birth reflects foundational responses to intrauterine hypoxia that produce reduced birth weights and lower body growth. The size of this effect varies significantly. Isolated from nutritional status, however, birth weight reduction appears directly correlated with length of residency at high altitude. Among indigenous groups, reduced birth weight is greatest in the Americas.

10.4.2 Childhood and Adolescence

After birth, children at high altitude tend to remain small for age. Prepubescent Nepalese Sherpa children, living between 3400 and 3800 m, are the shortest and lightest indigenous populations, while Sichuanese Tibetan children living at 3100 m are the tallest and heaviest. European Bolivian children living at 3600 m are the largest non-indigenous. While a portion of these differences reflect nutritional status, all high-altitude samples of children, regardless of ancestry and socioeconomic or nutritional status, are markedly shorter and lighter than US reference samples, with reduced skeletal muscle. Similar trends have been found in comparisons of genetically similar populations at high and low altitude, which argues for an independent effect of hypoxia.

Differences in attained growth partly reflect developmental delay. By puberty, skeletal maturation lags by 20% in both Tibetan and Andean children. Both groups approach US standards by 20 years of age.[29,51,52] Ethiopian children, by contrast, show smaller delays, reaching about 1 year at 12 years of age, with a velocity pattern comparable to Quechua children through most of childhood.[53] Both Quechua and Ethiopians were more advanced in hand–wrist skeletal age than Tibetans or Nepalese–Tibetans.[54]

Uniquely, Ethiopian children's maturational status catches up to chronological age in their sixteenth year. This has been variously attributed to reduction in disease stress in the Ethiopian highlands, to the moderate altitude (3000 m) at which these children live or to genetically unique physiological adaptations.[25,54,55] Delayed maturation followed by "catch-up" has also been viewed as part of an adaptive complex to inhibit growth of actively metabolizing lean tissue characteristic of adolescence.[29]

Estimates of the impact of high altitude on sexual maturation vary from little or no effect in Ethiopia, to small delays in the order of 6–9 months in Chinese or Tibetan populations, to over 1 year in the Andes and Nepal.[25,53,56] One study found moderate to profound delays among all high-altitude groups, with age at menarche ranging from 14.6 years for Ethiopian girls to 18.1 years for Sherpa girls and 16.1 years for Tibetan girls.[54] The only study to compare sexual maturation of genetically similar groups at low and high altitude found that Bolivian girls of European ancestry had a 0.8-year delay in menarche attributable to hypoxia relative to indigenous girls.[56]

Such wide variation in children's growth and maturation, given a constant hypoxic load, has led many investigators to cite nutritional stress as the larger causal factor, particularly in differences between indigenous and immigrant populations.[11,57–64]

In the clearest example of this, privileged French schoolchildren living at 3200–3600 m in La Paz, Bolivia, were 6 cm shorter than US reference standards, but 13 cm taller than their poorer Bolivian peers. The French contrast with US standards argues for an independent hypoxic effect, while the larger French advantage over Bolivian peers demonstrates the independent contribution of nutrition or factors such as access to health care. Importantly, growth status of the French children was related to their length of residence at high altitude; those with the shortest exposure were nearly 4 cm taller than those with the longest.[62]

In Central Asia, the picture is more complicated. Stunting, or reduced height for age by World Health Organization (WHO) standards, of Tibetan children increases with altitude, after control for nutritional and socioeconomic variables. Above 4000 m, over a quarter of all children were found to be stunted. By contrast, wasting, or reduced weight for age, was attributed to nutritional status, rather than hypoxia, except for the youngest children living above 4000 m.[65] Linear growth, then, appears particularly sensitive to hypoxic stress.

Differences between Tibetan and immigrant Han children are not systematic. In some studies,[64] Tibetans had more height and muscularity only at higher altitudes. Compared to lowland peers, Han were lighter and shorter. While they did not have larger chests, their lung volumes were greater, and they had elevated hemoglobin only at the highest altitudes.[66] In other samples,[61,62] Tibetan boys in mid-childhood were significantly taller, heavier and fatter than Han schoolmates of either sex, with higher vital capacity and percentage blood oxygen.

Urban–rural or sex variation in access to health care or food, rather than income per se, may account for some of the observed differences in nutritional status.[67] While suburban Tibetan boys in Sichuan were the largest, heaviest and most muscular among both sexes of four ethnic groups, urban Tibetan boys in Lhasa (3670 m) were systematically shorter and leaner, with lower body mass indices (BMIs) and skinfold thicknesses, than their female peers, and comparable to Han children. Unexpectedly, they also were smaller than either sex at a higher but less urbanized Tibetan site.[68,69]

The impact of undernutrition at high altitude can become dramatic when associated with broader political upheaval or socioeconomic neglect. Despite substantial growth improvements over 35 years in neighboring regions of the same altitude, there was no evidence of a secular trend in size among cohorts of Quechua Peruvian children living at 4250 m in an area torn by civil war.[70] Stunting and wasting were less common, but stunting still reached nearly 60%. Differences between these children and genetically similar peers elsewhere at the same altitude patently are nutritional, rather than hypoxic.

Data are rarer from high-altitude regions outside the Tibetan Plateau or Andean altiplano. Saudi children born and raised at 3000 m were lighter and shorter than National Center for Health Statistics (NCHS) medians, but their BMIs were similar before late childhood,[71] indicating a balanced impact on size and weight.

Indian-Tibetans born and raised at moderate to high altitudes were taller and heavier, and had thicker skinfolds than their peers in Tibet, but had similar elevated NO production. At 3521 m, they showed a pattern of leg growth retardation reported elsewhere.[72] Ethiopian children at 3000 m were closest to US sea-level references for height or weight. After mid-childhood, boys also were systematically taller than lowland peers, while girls and younger boys showed no significant differences. Compared to Peruvian or Nepalese Tibetan children, however, Ethiopians had reduced summed skinfolds and markedly lower chest circumferences, reflecting a more linear build.[54]

Overall, then, reductions of growth in size and weight at high altitude reflect independent contributions from hypoxia and undernutrition. How these are apportioned varies according to the parental gene pool, length of residency at high altitude, and balance between availability of oxygen and calories. Where the effects of nutrition can be controlled for, children's linear growth in Africa and Central Asia appears to be somewhat less affected by hypoxia per se than in the Americas.

10.4.3 Changes in Shape and Proportion

Finally, children's body proportions and shape appear to be influenced by high altitude. Across several Tibetan samples at 8 to 12 years of age, from 3000 to 4100 m, axial proportions including stature and lower leg length relative to stature were independently determined by oxygen availability, while stature, sitting height, chest circumference and arm proportions were independently influenced by caloric status.[67] Compared to Han peers, Tibetan children had longer lower legs,[60,61] although Han with the highest forced vital capacity (FVC) had leg proportions like those of average Tibetans[60] (see also refs 73 and 74). This suggests some overlap in adaptive efficiency that may reflect length of residence.

Andean children's axial proportions respond differently. Rural Aymara children averaged longer trunks relative to their stature, that is, shorter legs, compared to urban European ancestry peers. However, there was significant overlap in trunk to leg proportions between the two groups of children, and across ages, which could reflect maturational timing or adaptation.[75]

Larger chests are a consistent feature in high-altitude children, although the magnitude of the effect varies across regions. Prepubescent Ethiopian and Qinghai Tibetan boys have the most slender trunks relative to height, while Quechua boys have uniquely large chest circumferences for their size.[27,57,71,72]

Chest growth reflects functional adaptations. Children at high altitude typically have up to 1000 cm^3 greater FVC, and 500 cm^3 greater residual volume. Andean children show the most dramatic chest growth. At 4259 m, Peruvian children's and adolescents' chest circumference and FVC runs over 2 cm above US reference standards. Their residual volume is nearly 80% more than US standards.[76] Often mischaracterized as "dead air space", the residual volume actually represents a buffer of oxygenated air to

buffer against localized hypertension.[26] It has a higher heritability, and appears to be under active selection. Vital capacity is more representative of phenotypic plasticity; it will show dramatic increases in immigrants. Both compartments drive growth in chest dimensions.

Changes in chest size and function are less dramatic in Asia. Chest circumference is larger in Tibetan than Han children.[69] Chest length, correlated with FVC, increases with altitude in Tibetan children and adolescents, as does chest circumference.[71,72,77,78] At similar altitudes, immigrant Han children show significant changes in lung volume, but not chest dimensions.[64,66] Tibetans demonstrate significantly greater residual volumes than Han, while having more similar vital capacities.[25] However, despite their larger chests, blood oxygen saturation was only slightly greater among Tibetan boys. This may reflect Tibetan reliance on greater blood flow rates, rather than just on oxygen per unit blood, to combat hypoxia.[77,79]

Populations also differ in how altitude affects the timing of chest and lung growth. Andean populations showed increased velocity of trunk growth immediately upon birth, while European children in the same environment did not.[29,58,80] Moreover, chest circumference in Andean populations appears to expand into the third decade of life.[76] This latter effect has also been shown in Bod children of India at 3514 m,[25] and Ethiopian children at 3000 m,[53] but not Russian children from the Tien Shan region of Kirghistan (cited in Frisancho[25]).

Thus, while both indigenous and immigrant children ultimately produce larger chests and higher lung function than lowland peers, indigenous growth responses begin earlier and remain more profound. These increases, taken with enhanced lower leg growth, appear to be signature adaptive responses in body shape and proportion to hypoxia alone.

10.4.4 Molecular Control of Adaptation and Growth

Overall, variation in morphological growth within and between high-altitude regions suggests disparate gene pools confronting the same environmental stress. While Tibetan and Andean populations achieve basal metabolic rates and other measures of oxygen demand similar to lowlanders, they achieve them quite differently. From birth, Tibetans have significantly higher resting ventilation rates, reaching 15 liters per minute in adults, compared to 10.5 l/minute for Andeans, and adults show double the hypoxic ventilatory response to experimental stress.[77] Surprisingly, Tibetans do not develop local pulmonary hypertension, an otherwise universal mammalian response to hypoxia, nor do they develop enlarged chests as a result of obstructed pulmonary blood flow.[25,77] Blood flow is higher for Tibetans than immigrants from the second trimester of gestation through adulthood because of system-wide vasodilatation triggered by higher NO secretion by the arterial epithelium.[38] Finally, Tibetans show a greater density of muscle capillary beds, which enhances diffusion to cells.

By contrast, Andeans support morphological growth through elevated hemoglobin levels, enhanced lung volume compartments and total blood oxygen saturation relative to Tibetans. Andean populations show only mildly enhanced NO delivery, and demonstrate local pulmonary hypertension from birth; by adulthood clinical pulmonary hypertension and various cardiac myopathies are common.[28,76]

A third pattern of adaptation to hypoxia is shown by Ethiopians on the Semien Plateau. From 2 years of age onward, their linear build and some physiology, such as NO responsiveness, resemble Tibetan children. But unlike Tibetans, they also manage oxygen saturation that attains typical lowland US values. In the words of one investigator, it is "as if the Ethiopian sample were not living at high altitude".[55]

If we track growth outcomes to their sources, molecular mechanisms underlie the populational differences described above. From embryogenesis through adulthood, cellular trade-offs between oxygen tension and glucose metabolism are mediated by hypoxia inducible factor-1 (HIF-1) and HIF-2. HIF-1 is an evolutionarily conserved transcription factor independently triggered by hypoxia and heightened NO production. The body's primary angiogenic mediator, HIF-1 triggers early circulatory development in the naturally hypoxic environments of embryonic and fetal tissue. Postnatally, it orchestrates new vessel growth in the hypoxic conditions of a wound, organ lesion or bone fracture.[81]

HIF-2 is structurally similar, with some overlapping functions,[82] but is uniquely involved with maturation of the lung epithelium and blood cell production, and is thus linked to NO production via the epithelium.

Both factors collaborate in promoting gene expression for cartilage matrix deposition in bone and meniscus[73,78] via vascular endothelial growth factor (VEGF), which up-regulates blood vessel growth factors. By mediating how much blood is available, VEGF paces the maturation of all bone cells. Osteocytes and NO, in turn, can up-regulate HIF. The feedback has been termed angiogenic–osteogenic coupling.[74] HIF factors are particularly active in cartilage, where normal oxygen tensions are between 7% at the outer surface and 1% at the inner core.[39,78,83] Thus, skeletal growth under hypoxic conditions is HIF dependent.

A cellular trade-off between calories and oxygen occurs because HIF-1 also promotes glucose transporter-1 (GLUT-1), which increases uptake of glucose for anaerobic glycolysis.[84] Because anaerobic glycolysis is less efficient, there will be reduced energy available for bone growth.[46] Under normoxic conditions, HIF systems are damped throughout the body. Skeletal growth will be primarily limited by glucose availability. However, even comparatively mild levels of hypoxic stress to fetuses may trigger direct HIF inhibition of glucose metabolism in their mitochondria, which will limit growth.[44] For a fetus, then, high altitude may have a significantly lower stress threshold. Lower limb vulnerability to hypoxia, which begins in utero, may reflect an overlay of hydraulic

compromises, arising out of bipedalism, set upon basic mammalian predispositions towards enhanced perfusion of the forebody to defend brain metabolism.[40,41,68,69]

The genes controlling these molecular growth trade-offs differ among populations. Quantitative genetic approaches have not identified a major gene complex that differentiates between high- and low-altitude Andean Indian populations' responses to hypoxia. Their growth patterns may represent lowland developmental plasticity extended as far as a lifetime at high altitude permits. Tibetans, by contrast, have two rapidly evolving gene variants in the EPAS1 (HIF-2) system that now characterize over 90% of all Tibetans.[85] These variants may reduce the need for accelerated lung or chest growth, or right ventricular hypertrophy, characteristic of Andean and other populations at high altitude by 3 months of age. Tibetan maturational timing is slowed, but the etiology — hypoxic or caloric — remains unclear. Unfortunately, we have no comparable molecular studies of Ethiopians. Their growth patterns suggest adaptive mechanisms that have achieved high equilibrium frequencies. Ethiopian growth patterns could reflect an African stamp on original central Asian adaptive complexes reflected in their 20% Asian mitochondrial DNA.[25]

We are confronted, then, with an embarrassment of windows into dissimilar populations of growing children. Central Asian and African adaptive responses to hypoxia may be more evolutionarily effective, if measured by comparatively better growth outcomes and lower morbidity and mortality attributable to hypoxia. However, all children pay a cost for living in thin air. Calculating that cost, and apportioning it among various environmental stressors, remains daunting.

10.5 SLEEP

Sleep is at the intersection of environmental and internal influences on growth and human biology. Inasmuch as society and its behavioral norms influence sleep characteristics, it can be considered an environmental influence and so is included here.

Sleep duration and quality have been associated with a variety of physiological systems, including immune function, glucose metabolism, neurobehavioral performance and hormonal profiles, which indicates that sleep plays an important role in human health. Total sleep duration per day declines from birth to adulthood ranging from an average of 14 hours at 6 months of age to an average of 8 hours (SD 0.8 hours) at 16 years of age.[86] Sleep is comprised of two major sleep stages, rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep. Sleep stages develop in utero, at approximately 28—32 weeks' gestational age.[87] The amount of REM is greater earlier in development, and increases from 30—32 weeks' gestational age until 1—2 postnatal weeks.[87] By 2 years of age, REM sleep is established at 20—25% of the total sleep time, and this proportion remains stable throughout adulthood.[88]

Many hormones related to growth are affected by the sleep–wake cycle, including growth hormone (GH), luteinizing hormone (LH), testosterone, follicle-stimulating hormone (FSH) and prolactin (PRL). In adult men, the largest and often the only pulse of GH occurs shortly after sleep onset. In women, smaller daytime GH pulses are more frequent, but the sleep-onset pulse, while reduced in amplitude relative to that observed in men, is usually present.[89] In children, GH levels are typically higher during sleep than during wake, with a peak occurring shortly after sleep onset.[90–92] When sleep is interrupted by waking, GH secretion is abruptly suppressed.[89] An early study observed that among prepubertal children, In children, GH was secreted only during sleep while among pubertal adolescents and young adults GH was secreted during both wake and sleep, but the amount secreted during sleep was approximately double the amount secreted during wake.[93] A study in infants ranging in age from 1 week to 12 months found that GH levels were higher during sleep than wake only after the age of 3 months.[94] Thus, the secretion of GH is tightly coupled to the onset of sleep in children as young as 3 months up through adulthood. LH levels also appear to increase during sleep in pubertal children but not prepubertal children or young adults.[95,96] This sleep-induced increase in LH will occur even if sleep occurs during the daytime, indicating that it is not simply a circadian effect.[97] Furthermore, in pubertal boys, there is a marked increase in testosterone secretion during sleep, which appears to be dependent on the increased LH secretion.[96,98] One study also demonstrated a sleep-related increase in FSH in boys and girls in late puberty.[95] In adults, levels of PRL are normally lowest at midday and increase slightly throughout the afternoon, with a major nocturnal elevation shortly after sleep onset.[89] Regardless of time of day, sleep onset stimulates release of PRL; however, maximal simulation occurs only when sleep occurs at night.[89] A sleep-dependent release of PRL in both prepubertal and pubertal children has also been observed.[89] Given the invasive nature of frequent blood sampling, only a few studies have examined the relationship between sleep and hormonal secretion, but they have generally found that sleep is associated with the release of many hormones involved in growth and development.

Few studies have examined the relationship between sleep and linear growth or sexual maturation prospectively. Two studies examined the relationship between sleep duration and linear growth but found no association.[99,100] A small study of four children aged 1–3 years did observe increases in both sleep and growth after treatment for psychosocial dwarfism,[101] but whether there is a causal link between the changes in sleep and changes in growth cannot be determined. Prospective studies need to use objective measures of sleep and anthropometry among children of varying ages to determine whether sleep duration or quality can affect growth.

Several changes in sleep behavior typically occur during pubertal development. For example, total amount of sleep obtained per night decreases, which is associated with an increase in daytime sleepiness.[99,102–104] The decrease in amount of sleep obtained in

adolescence, however, does not reflect a decrease in sleep need. In fact, sleep need appears similar across childhood and adolescence and is estimated to be approximately 9 hours.[102,105] The timing of sleep becomes delayed during pubertal development, which means that propensity to sleep occurs later in the evening and spontaneous awakening occurs later in the morning.[102,106] Owing to social commitments, such as school, adolescents must often wake earlier than spontaneous awakening and this probably explains both the shorter sleep durations and increased daytime sleepiness associated with greater sexual maturation. Thus, sleep changes during sexual maturation, but whether the timing or tempo of maturation is affected by sleep is not known.

The duration and quality of sleep have also been associated with body weight and BMI. Over 65 observational studies have found significant cross-sectional associations between short sleep duration and increased BMI in both adults and children (see Refs 107–109 for reviews). Some studies have also found that poor subjective sleep quality was associated with higher BMI.[110,111] Two meta-analyses analyzed data from cross-sectional studies in children and both found significant associations between short sleep duration and increased odds of being obese.[112,113] There have also been a few prospective studies of sleep and weight gain in children, which reported that shorter sleep durations or greater sleep problems were significantly associated with increased weight gain or risk of obesity.[114–120] Experimental studies of sleep restriction in young adults have suggested that one potential mechanism for a link between sleep and weight gain is dysregulation of hormones that contribute to appetite regulation, including a reduction in leptin, an appetite suppressant, and a concomitant increase in ghrelin, an appetite stimulant.[121,122] Similar studies have not been conducted in children. Nonetheless, the prospective studies suggest that short sleep duration is associated with increased body weight in children, which could increase the risk of developing obesity.

In summary, several hormones that are important for normal, healthy growth and development are associated with sleep. Furthermore, insufficient sleep may be a risk factor for the development of obesity, the rates of which are increasing dramatically for children and adolescents worldwide. Thus, more research is required to understand better the impact of chronic sleep restriction and impaired sleep quality in children and adolescents. Finally, since bedtimes are a volitional behavior, researchers need to examine cultural variation in sleep practices, particularly with respect to children.

10.6 POLLUTANTS

Pollution is usually defined as unwanted materials (e.g. lead, mercury, particulate matter) or energy (e.g. noise and radiation) produced by human activity or natural processes such as volcanic action. Anthropogenic pollutants are produced from power plants that generate energy, manufacturing industries, transportation, the construction of homes

and factories, and even agriculture. Once created, pollutants are dispersed globally to virtually all populations by wind and water currents, and through the food chain.

In the past most of our knowledge of biological effects of pollutants came from occupational studies, but the information was not very generalizable as it usually concerned effects of large exposures on adult males. Developments in measurement technology have made it possible to make accurate measurements of low levels of pollutants using very small biosamples. Pollutants are now routinely detected in pregnant women, newborn babies and children, and we need to understand their effects on the developing organism when environmental insults can have irreparable, long-lasting effects. Fetal programming (see Chapter 12), the impact of environmental factors on the fetus that affect its functioning postpartum and its health in later life, can be thought of as a reformulation of reproductive toxicology that includes nutritional insults as well as chemical ones.

The study of human development and toxicants is based on observation without modifying exposures, since an experiment in which exposure is randomized to subjects is obviously unethical. Purely observational studies yield statistical associations and these must be judged in terms of the likelihood that the association is based on biological cause. There are six commonly used criteria for judging the causal basis of statistical associations (Box 10.1), and studies of growth and environmental factors should be designed to meet these criteria as much as possible.

All of the listed criteria depend on the accurate and reliable measurement of exposure. The best way to assess exposure is to measure the pollutant of interest in the person. For example, in a study of lead, it is best to measure lead in the blood or bone. An inexpensive but far less accurate method of assessing exposure is the substitution of a measurement made in a geographical zone, such as a postal zone, for the exposure of every child living in the zone. However, people in one zone are likely to experience different amounts of true exposure and grouping them together and using an average value leads to misclassification. This produces large errors in the independent (exposure) variable and less statistical power to detect effects. Too often studies of growth and pollution are forced for economical reasons to use this latter method, but effects on growth are more likely to be accurately determined if we can employ the most accurate

Box 10.1 Criteria for judging the causal basis of statistical associations

- A strong association
- Biological credibility to the association
- Consistency with other studies
- Compatible sequence of cause and effect
- Evidence of a dose–response relationship

measures of exposure. Despite the challenges in studying pollutants, there is now considerable evidence that human physical growth and development are sensitive to several pollutants including lead, the components of air pollution, organic compounds such as polychlorinated biphenyls, as well as some forms of energy such as radiation and noise.

10.6.1 Cigarette Smoking

Cigarette smoking is a perfect example of an anthropogenic influence on growth and development. Exposure is a function of human behavior, the exposure composition is complex, and human experience with smoke is fairly recent, although some could argue that smoke is the oldest pollutant.[123]

Cigarette smoke contains a large variety of compounds including carbon monoxide and cyanide. These compounds can cross the placenta and affect the fetus, and second-hand cigarette smoke may affect children in households with smokers.[124] Postnatal exposure to cigarette smoke may also affect growth, but this problem has not been studied sufficiently.

After gestational age, maternal cigarette smoking is the single greatest influence on birth weight in well-off countries.[125] In most populations suffering from nutritional stress, very few women smoke during pregnancy, so the effect of smoking is minimal or absent. Women who smoke during pregnancy have babies weighing on average 200 g less than babies of non-smokers and the reduction in birth weight is related to the number of cigarettes smoked. This dose—response relationship is good evidence for a causal relationship between smoking and prenatal growth. Gestation length is reduced by only 2 days or less, which cannot account for the birth-weight decrement. When birth weights of smokers' and non-smokers' infants are compared at each week of gestation from weeks 36 to 43, smokers' babies consistently have lower mean birth weights. Just living with a smoker may affect birth weight, as women whose husbands smoked had lower birth-weight babies.[126,127]

The reduction in mean birth weight is part of a downward shift of the entire distribution of birth weights. Thus, the frequency of LBW (less than 2500 g) is more common among smokers, again irrespective of gestational age, and it is approximately doubled among smokers.

Maternal smoking also is significantly associated with shorter body lengths (about 1 cm), reduced arm circumference and, in some studies, slightly reduced head circumference.[128—131] The sizes of the decrements depend on the amount and timing of cigarette consumption by the mothers in the sample. Weight growth is strongly affected by smoking in the last trimester. In one longitudinal study using repeated ultrasound imaging, biparietal diameter of the head increased significantly more rapidly among fetuses of non-smokers from the 28th week of gestation onwards, i.e. starting near the beginning of the last trimester of pregnancy.[40]

The effect of quitting smoking after conception also informs us of when smoking acts to reduce prenatal growth. Quitting before the fourth month of pregnancy is thought to reduce or remove the effects of smoking. However, quitting is more common among light smokers than heavy smokers. When both the amount of smoking and the quitting are considered, very heavy smokers who quit may not fully lower their risk of LBW.[132] However, from a practical point of view, quitting or reducing smoking is advised for all women who smoke and who are pregnant or who may become pregnant, because smoking has such a strong, detrimental effect on the fetus.

The primary constituent of tobacco smoke is carbon monoxide. Carbon monoxide, with an affinity for adult hemoglobin 200 times that of oxygen, has an even greater affinity for fetal hemoglobin. It is estimated that if a mother smokes 40 cigarettes per day there is a 10% concentration of carboxyhemoglobin equivalent to a 60% reduction in blood flow to the fetus. Thus, cigarette smoking exacerbates fetal hypoxia, which has some similarities to high-altitude hypoxia. In fact, placenta ratios are larger among smokers largely owing to the reduction in birth weight, as they are among high-altitude births. Some studies have noted that the placentas of heavy smokers are heavier than non-smokers' placentas,[133,134] a finding consistent with effects seen at high altitude.[33] However, other studies have found no difference in placenta size associated with heavy smoking and the nicotine content of cigarettes smoked.[130,135] Smokers' placentas also are thinner, with larger minimum diameters.[133] Some of these changes in placental morphology may be adaptive given the reduced oxygen-carrying capacity of the blood, but other changes, such as calcification or ones indicative of aging or chronic ischemia (lack of blood flow) in the placenta do not appear to be adaptive.

Cigarette smoke also contains nicotine, which stimulates adrenal production of epinephrine, norepinephrine and acetylcholine, and this results in less uteroplacental perfusion (blood flow through the uterus and placenta). It also can act on the fetus directly to increase fetal blood pressure and respiratory rate. In addition, cyanide, lead and cadmium are contained in cigarette smoke and are all toxic.[136] Smoking can also affect hormone levels[137,138] and this, in turn, could affect prenatal growth.

It is tempting to think that smoking may not act through any of these means, but indirectly by reducing maternal appetite and weight gain, but this is not the case. Studies have compared weight gains of smoking and non-smoking pregnant women and found that weight gains are similar. Other studies have controlled for weight gain by matching for weight or through statistical procedures, and the effect of smoking on size at birth is still present.

Postnatal effects of cigarette smoking are less well studied and less clear. Follow-up studies of smokers' offspring have difficulty separating effects that may develop from being exposed to cigarette smoke in utero from the effects of postnatal exposure due to living with adult smokers. Ideally, to research the effect of postnatal smoking, one would study children whose mothers did not smoke during pregnancy but who began smoking

soon after giving birth. Few mothers meet these conditions, leaving most researchers to study children whose mothers smoked during pregnancy and who have continued to do so after the baby was born. Although some studies have not found lasting effects from birth,[139] many other studies have. The difference may be due to the extent to which other influences on growth are controlled or to the size of the sample. Using a sample of a few hundred children, Hardy and Mellits[140] found a 1 cm difference in length at 1 year of age that, though small, was statistically significant, but no differences at 4 and 7 years of age. In studies using larger samples, differences in height of about 1.5 cm at 3 years[141] and 5 years of age[142] were found. Analysis of the National Child Development Study (NCDS), which is a very large national sample from Britain, detected a deficit of approximately 1 cm in children's heights at 7 and 11 years associated with maternal smoking.[143] In one study of 3500 adolescents, the heights of 14-year-old girls were reduced by an average of nearly 1 cm, which was statistically significant, but the boys' heights did not differ significantly.[144] However, the NCDS sample found a small but significant reduction at age 16 years in male heights (about 0.9 cm), but not in females.[145] It seems that the difference of 1 cm that is present at birth becomes a smaller fraction of the variation in height that increases as individual differences in the tempo of height growth are expressed and reach their greatest magnitude at puberty.

The effect of passive smoking is small but significant in large samples. Rona and colleagues[146] examined the heights of children in relation to the number of smokers in the household (none, one or two) and corrected for birth weight to remove the effects of maternal smoking during pregnancy. Height declined with more smokers in the home, suggesting that passive smoking may affect postnatal growth.

Adipose tissue growth may also be reduced in relation to maternal smoking during pregnancy and postnatal exposure to cigarette smoke.[147] This finding is consonant with observations among adults that smokers are leaner[148] and their fat distribution tends to be more centripedal (located on the torso).[149,150] When adult smokers quit smoking, they add fat and attain a more peripheral or gynoid distribution (on the thighs, hips and arms). This, in turn, is consistent with the observation that cigarette smoking contains anti-estrogenic compounds such that female smokers tend to have fat patterns that resemble those more typical among males. The difference seen in 6–11-year-old children may be a late expression of an effect of prenatal exposure, or may be a response to postnatal exposure to cigarette smoke. In either case, adipose differences have not been found at birth.[129,151]

There is no doubt today that cigarette smoking is a powerful cause of reduced prenatal growth. Deficits are greatest in weight at birth but these appear to be made up during childhood, whereas the small deficit in length is not. Postnatal exposure to second-hand cigarette smoke seems to reduce height growth slightly, although more replication studies are needed. All studies of growth should consider the effects of smoking carefully, especially if the subject is the growth of the fetus.

10.6.2 Air Pollution

Air pollution is a ubiquitous form of pollution and a very heterogeneous category of materials. Most studies compare two or more settlements that differ in the severity of air pollution and many control well for differences in socioeconomic status. Most, but not all, of these studies report that height and weight growth are more favorable in less polluted areas.[152–155] Slower skeletal maturation has been observed in several studies.[155–157] It is possible that air pollution exerts an effect like high-altitude hypoxia, limiting the oxygen available for growth. Mikusek[158] found that girls from an air-polluted town were delayed in all growth dimensions except for chest development, a selective effect similar to the sparing of chest circumference growth seen in some studies of high-altitude Andean children.

The effect of air pollution begins prenatally. An early study of birth weight in Los Angeles, California, found that weights decreased in relation to the severity of the air pollution, and the effect was evident after controlling for some of the other large influences on birth weight (mother's cigarette smoking and socioeconomic status).[159] This finding has been well replicated,[160–162] but there also are a few instances where no effect has been found.[163] Some variation in results could be due to variation in the characteristics of the air pollution itself. The most recent work has tried to determine which components of air pollution may be responsible, the suspended particulate matter or the gases (sulfur oxides, nitrogen oxides and ozone), but the answer is not yet clear.

10.6.3 Organic Compounds

Organic pollutants include many insecticides and herbicides that have been used in agriculture and pest control. Dichlorodiphenyltrichloroethane (DDT) is a pesticide, highly effective in controlling mosquitos, which was banned in the USA in 1972, but is persistent and its metabolite (DDE) is found in the blood of many populations. Other pollutants were manufactured for use in various industries [e.g. polychlorinated biphenyls (PCBs), phthalates], and others, such as dioxin, are unintended by-products of manufacturing. Phthalates are plasticizers used in bottles, toys and personal care products. PCBs are a large group of similarly structured compounds with variation in toxicity and persistence in the environment and in the body. Some forms are very similar to dioxin. Polybromated diphenyl esters (PBDEs) are fire retardants added to a large variety of consumer items that leach into surrounding materials and now can be detected in many populations. Organic pollutants such as PCBs, dioxin and DDT are lipophilic; they are stored in fat cells and can be retained for years. They cross the placenta, and lactation is a significant source of exposure. They are also found in dietary items such as fish, meat and dairy products.

PCBs may affect endocrine function, physical growth, maturation and/or cognitive or behavioral development of children and youth. Evidence of the effects of PCBs in

humans comes from two types of study: studies of *acute* poisoning, either food poisoning or an occupational accident, and studies of *chronic* low-level exposures, usually from ingestion of foods with slight but measurable contamination.

Ingestion of rice oil contaminated with a mixture of PCBs, dioxin and dibenzofurans poisoned thousands of adults and children in Japan in 1968 and in Taiwan in 1978–79, producing diseases called Yusho and Yucheng, respectively. Yusho/Yucheng infants have had higher rates of mortality and lower body weights at birth.[164] Even children born long after their mothers were exposed to the contaminated oil were more often born prematurely and small at birth,[165] probably because during gestation they were exposed to the toxicant mixture that had been stored in their mothers' fat tissue. Reduced postnatal growth also characterizes Yusho/Yucheng children.[164,166,167]

Studies of children born to women exposed to smaller amounts of PCBs over a long period have also found growth deficits. A common but not universal finding is that birth weight is reduced in response to PCB exposure.[168–173] The effect seems not to be due to prematurity but to less growth during gestation. Head circumference may also be reduced.[172] Three studies have related reduced birth weight to fetal exposure to dioxin and dioxin-like compounds.[174–176] PCB levels and BMI are related early in life[177] and at puberty.[178] DDE, a metabolite of the insecticide DDT, has been related to reduced birth weight and height in several studies,[179] but with increased height and weight for height in others.[177,178,180–182]

Not all studies agree (see, for example, Boas et al.[183]). It is important when interpreting conflicting results to account for differences in exposure among the studies. Certainly one would expect a smaller effect or none at all when the exposure is very low, and it is difficult to ascertain how exposure levels compare across studies because measurement techniques have changed substantially and only the most recent studies measure the contaminant compounds in similar ways. In addition, different effects may stem from differences in the timing of exposure: prenatal versus postnatal. Children exposed to PCBs from maternal consumption of fish from the Great Lakes were significantly lighter at 4 years of age, though not at 11 years of age.[184] The reduction at age 4 was related to the PCB level at birth, reflecting prenatal exposure, but not to their current PCB level. Another longitudinal study found greater height in girls at 5 years of age in a cohort in which there had been differences in size at birth.[168]

Clearly, not all studies of humans agree as to the size and direction of effects that these toxicants have. This creates questions about the influence of differences in levels of exposure, differences in the timing of exposure (prenatal or postnatal) and differences in the mixtures of compounds to which the sample was exposed. Excepting occupational exposures, mundane exposures tend to be a mixture of several compounds. While we tend to group all these persistent organic pollutants as "toxic", we have learned not to expect them to have similar effects on growth.

We do know that the alterations in growth are best explained as due to interference with hormonal signaling. Further, we know that different compounds affect signaling differently depending on the timing of exposure and their structure as some are agonistic and some antagonistic. Many studies of non-human animals have shown that hormone activity can be altered following exposure to PCBs and related compounds. Thyroid hormone signaling is especially important for normal physical and mental growth and development. Neurological effects are the most consistently reported effects of chronic PCB exposure.[185–187] A study of Mohawk adolescents, 10–17 years of age, found the combination of reduced thyroxine levels and increased thyroid-stimulating hormone levels (this usually signals low thyroid activity) in relation to levels of persistent PCBs that reflect past exposure, but not in relation to PCBs more reflective of current exposure. This suggests that prenatal or neonatal exposure may be influential.[188] In this same group, there were alterations in performance on some cognitive tests and particular effects on memory.[173]

Studies of the effects of phthalates in children have intensified recently as the material is found in more products and more populations. Effects of phthalates on the thyroid have been reported.[183] Growth and sexual development can also be affected.[183,189–194]

Many types of organic pollutant structurally resemble sex steroids as well as thyroid hormones. The possibility of deranged hormonal signaling of sexual development and reproduction has been a controversial area of research, but there is now sufficient evidence that it occurs in humans. Several studies conducted by different research groups and with different populations have reported that exposure to some pollutants accelerates the development of puberty, although the finding is not universal.[195–197]

Whether the effect is one induced by prenatal or postnatal exposure, or both, is not clear. Newborns were found to have significantly lower testosterone and estradiol levels in relation to their mothers' levels of dioxin, dibenzofuran (similar to dioxin) and dioxin-like PCBs.[185] Follow-up of boys in the Yucheng cohort who had substantial exposure to dioxin-like compounds showed reduced testosterone levels and increased FSH levels but no difference in Tanner stage.[186] Preliminary results from the same cohort found significantly reduced penile lengths, a possible effect of their exposure prenatally when critical sexual differentiation and development is occurring.[187]

A related compound, PBDE, is a new pollutant of concern. In adult men it has been strongly and inversely associated with a measure of androgen, with LH and FSH, and positively with inhibin B and sex steroid binding globulin.[198] This result and other similar findings strongly suggest that chemicals in our environment can affect levels of hormones directly involved in reproduction and development. In true experimental studies of non-human animals endocrine disruption is clearly evident and this establishes the biological plausibility of the associations seen in observational studies of human populations.[199] Research on children and PBDE is just beginning. If the effects seen in adults are present in children, they certainly could affect growth and sexual maturation.[200,201]

There is sufficient evidence to be concerned about PCB exposure in children and the fetus. Especially convincing are the controlled laboratory studies of higher primates and rodents that show reductions in growth and alterations in sexual development that are dependent on normally functioning hormonal systems.[202,203] Although it is not known whether a low-level exposure will produce effects on child development, we do see that high exposures, such as those from food heavily contaminated with PCBs, can produce predictable effects, and the possibility that the fetus is especially sensitive to PCBs, even at low levels, remains a very viable hypothesis.

10.6.4 Lead

Lead has been a common pollutant since it was first added to paint and gasoline. In the USA, lead burdens are higher among urban, disadvantaged, minority children because of their residence in older areas characterized by dilapidated housing having flaking leaded paint and with older roadways where cars burning leaded gasoline deposited lead in exhaust fumes. People also are exposed to lead from their mothers through transplacental passage and lactation. Lead is a legacy pollutant that has been transmitted to each generation through biological and social pathways.

Studies often indicate that size at birth is reduced and gestations are shorter with increased lead exposure,[204,205] although some studies do not detect such differences, perhaps owing to uncontrolled confounding variables such as maternal nutrition.[206–208] Studies in Cincinnati, Ohio, and Albany, New York, found a reduction in birth weight of nearly 200 g in relation to the log of maternal blood lead level.[209,210] Other studies have found reductions in head circumference.[211] A study of 43,000 recent births in New York state found reductions in birth weights of 61 to 87 g depending on the level of maternal lead, 0 versus 5 mg/dl and 6 versus 10 mg/dl, respectively.[212] Results from this extremely large study remind us that the inconsistencies in findings of pollutants and growth often can be explained simply by differences in the exposures of the populations studied.

Studies of birth weight are facilitated by routine collection of birth weight as part of public health surveillance. Studies of postnatal growth are less common. The largest studies have used national survey data from the USA. Data from the second National Health and Nutrition Examination Survey (NHANES) data (1976–1980) involving about 7000 children less than 7 years of age showed that lead level was negatively related to stature, weight and chest circumference after controlling for other important influences on growth.[213] Compared to children with a blood lead level of zero, children with the mean lead level were 1.5% shorter at the mean age of 59 months. The second large study used a data set of 7–12-year-old children from the Hispanic Health and Nutrition Examination Survey (1982–1984). Children whose blood lead levels were above the median for their age and sex were 1.2 cm shorter than those with lead below the median.[214] The third study used anthropometric data from the Third NHANES

(1988–1994) for non-Hispanic children 1–7 years of age, and found statistically significant reductions of 1.57 cm in stature and 0.52 cm in head circumference for each 10 μg of lead in the blood.[215] An analysis of 8–18-year-old girls in NHANES III found that those with moderately high lead levels were significantly shorter.

Studies with smaller samples have also found growth decrements in height, weight and/or head circumference of similar magnitude, indicating that the associations between growth and lead reported for national samples of US children may be present generally.[216–218] Other anthropometric dimensions may also be decreased.[219] When lead levels are reduced in a neighborhood through public health efforts, child growth may respond positively,[220] which suggests that early growth decrements may be reduced if the exposure is reduced early in life.

These studies are cross-sectional, that is, lead and stature were measured simultaneously, and consequently one could argue (and some have) that short children are simply exposed to more lead. However, experimental studies of non-human animals show very clearly that growth is reduced following lead exposure, which supports the latter explanation.

There have been few longitudinal studies of lead and growth. In the Cincinnati study, higher maternal blood lead levels coupled with higher infant lead levels were associated with poorer growth.[221–223] Similarly, when the children reached 33 months of age, two groups of children had decreased stature: those with low lead levels prenatally but high lead levels from 3 to 15 months, and the children with high lead levels in the prenatal *and* postnatal periods.

A study of infants in Albany, New York, also found that when lead levels increased between the pregnancy (maternal) level and the infant's own level at 12 months of age, there was poorer infant growth in weight and head circumference.[224] Reduced infant weight gain in relation to lead has been found in other studies as well.[225] Not all studies agree and this may be attributed to differences in methods and/or levels of exposure or control for normal sources of variation such as diet, cigarette smoking, etc.[226]

Several large studies with good measurement methods and control of relevant confounders have established quite clearly that lead exposure is related to delayed menarche and delay in attainment of Tanner stages.[227–231] Among African-American girls in the NHANES III study, lead-associated delays in reaching Tanner stages ranged from 2 to 6 months depending on the Tanner stage, and menarche was delayed by 3 months.[228] A study of 10–16.9-year-old girls of the Akwesasne Mohawk Nation in northern New York found delays in reaching menarche related to lead level. Girls were delayed on average by 10 months if their lead level was below the sample median compared to the average for those above the median.[224,231] Pubertal onset in Russian boys was delayed by some 6–10 months.[230] One study of girls in Poland found contrary results: earlier menarche was associated with higher lead levels.[232] However, in this study lead was not measured in the individual, but in the environment, thus raising concerns

about the accuracy of exposure classification. Still, contrary results can reveal other influences and interaction effects, and if well constructed, should not be ignored.

A mechanism for the effect of lead on sexual maturation is not clear as yet, but one has been suggested through a study of girls in the NHANES III sample. Those with higher lead levels had lower levels of inhibin B, a marker of follicular development. Further studies into toxicants and sexual maturation are warranted to confirm this finding and elucidate the mechanism that produces the effect.

There is a better understanding of the mechanism for lead's effect on growth. Growth velocity can increase when children receive chelation therapy to remove lead from the body.[233] When children's lead levels have been reduced, their stimulated peak human GH levels are significantly higher compared to when lead levels are at a toxic level. In addition, among children with high levels of lead, insulin-like growth factor-1 is reduced with increasing lead level. These results help to make the statistical associations between lead and reduced height growth more understandable as true biological effects.

Over the past half-dozen years, more and more studies have shown relationships between lead levels and growth and maturation. Moreover, the effects are seen at quite low levels that would have been of little concern 20 years ago. This fact reinforces the idea that growth is sensitive to environmental inputs, including or especially anthropogenic ones, and at relatively low levels and through day-to-day, chronic exposures.

10.6.5 Radiation

High doses of radiation, as are used for some cancer treatments, do affect height growth.[234] In these studies radiation dose is both high and carefully measured, and the effect on growth is well established.

However, mundane exposure to radiation is far harder to measure. Individuals have difficulty recalling all their exposures to mundane sources (e.g. medical X-rays, airplane flights), thus introducing error in measuring exposure. One study found that women who had been exposed prenatally to medical X-rays were about 1.5 times more likely to experience menarche before the age of 10 years,[235] and others have detected postnatal growth retardation.[236]

In studies of people exposed through atomic bomb blasts, dose can be estimated by determining location in relation to the epicenter of the blast. Several studies have found that in utero exposure to an atomic bomb blast is associated with reduced head circumference, height and weight during childhood and adolescence and that the reduction is related to estimated dose.[236,237] One study of accidental exposure to a bomb test found that early postnatal exposure is detrimental as well.[238] In these early studies, maturation rate, if examined at all, was not affected significantly. The most recent work on growth and radiation examined growth at adolescence among survivors of the Hiroshima and Nagasaki atomic bombs.[239] From 10 to 18 years of age, total in utero

exposure was related to a reduction of several centimeters in stature, but it was not possible to see whether exposure in a particular trimester was especially damaging.

Microwave radiation is quite different from radiation from bomb blasts or cancer treatment, but is commonly experienced through mobile phone use. The growth of children and adolescents using mobile phones has not been studied as yet, but reports of increased sleep disturbance related to greater phone use point to a possible indirect effect on growth (as described in Section 10.5).[240]

10.6.6 Noise Stress

Noise is a classic physiological stressor used in countless laboratory studies to induce stress responses in experimental animals. Studies of humans show that noise, defined as unwanted sound, stimulates the classic stress response as well. Thus, studies of noise are studies of stress.

Several studies have examined prenatal growth in relation to maternal exposure to noise from the workplace and have found small effects on birth weight or, in one case, none at all.[241–243] Studies of airports, where noise stress may be more severe or better measured, find fairly consistently that birth weight is depressed in relation to exposure.[244–250] Two studies have found similarly sized reductions in birth weight related to aircraft noise and both studies found these effects among female births but not males.[246,250] Other studies have not examined effects by gender, but further research may determine whether the effects of noise stress are modified by this factor.

Evidence for an environmental effect on growth depends on different lines of evidence (see Box 10.1) and these are present among the studies of noise stress. Large sample studies that have compared groups differing in exposure have found that high maternal noise exposure is negatively related to birth weight in a fairly consistent dose–response manner (Figure 10.2).[249] Examination of the rate of LBW and the rate of jet airplane flyovers at Kobe airport when jets were first introduced demonstrates the temporal relationship between exposure and effect. Before the introduction of jets, the rate of LBW near the airport was lower than the rest of Japan, but as soon as jet flights began, the rate of LBW increased markedly and the increase continued to parallel the increased number of jet take-offs. The temporal association strongly suggests that the jet take-offs are causally related to the change in the frequency of LBW.

Studies of postnatal growth are very few, perhaps owing to the difficulty in estimating noise exposure for postnatal life. The first such study found reduced heights and weights among children exposed to high noise from an airport in Japan. More recent studies have found a reduction in height at 3 years of age (Figure 10.3) and a reduction in soft-tissue dimensions in children at 5–12 years of age.[251]

An effect of noise seems plausible based on what we know about the relationship of high noise to the stress response and the relationship between stress and growth. Noise

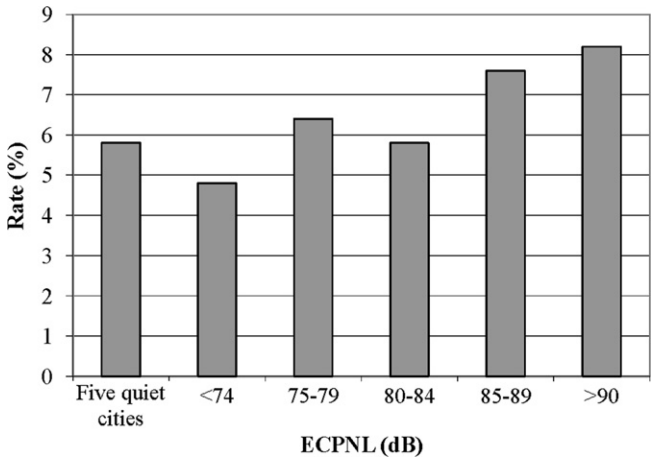

Figure 10.2 Percentage of low-birth-weight infants (< 2500 g) in 1969 according to mothers' exposure to aircraft noise measured as equivalent continuous perceived noise levels (ECPNL) (dB). *(*Source: *Adapted from Ando and Hattori.*[249]*)*

activates the hypothalamic—pituitary—adrenal axis in the same way as other stressors do (Figure 10.4). Noise stress stimulates the autonomic nervous system and the pituitary gland which, in turn, affects the adrenal cortex, the thyroid and the gonads. Cortisol, thyroid hormones and sex steroids all affect growth and development. Thus, an effect of noise on growth is biologically plausible. Since noise is a form of stress, studying noise exposure is a way of learning about the effects of other kinds of stress as well.

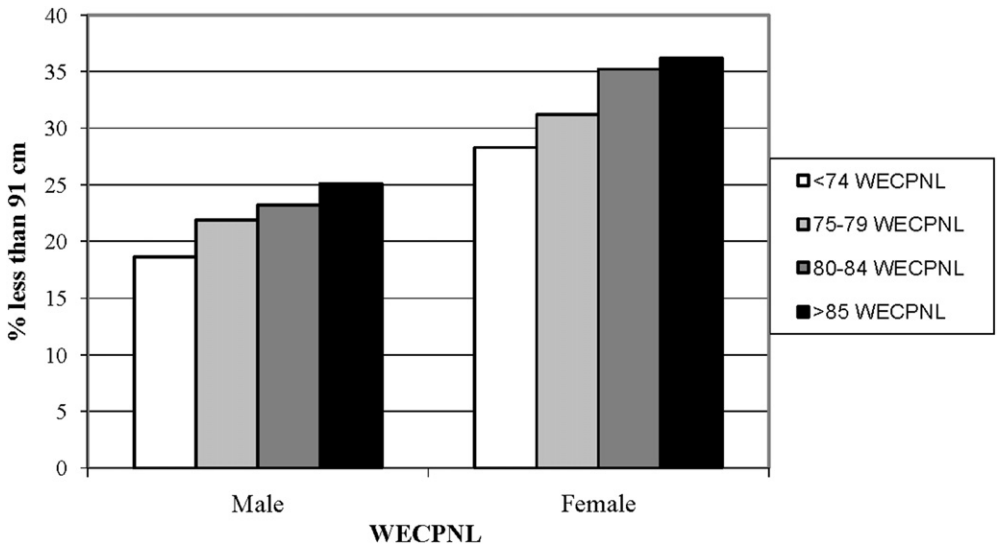

Figure 10.3 Percentage of 3-year-old children <91 cm tall by noise exposure measurement weighted equivalent continuous perceived noise levels (WECPNL). *(*Source: *Adapted from Schell and Ando.*[252]*)*

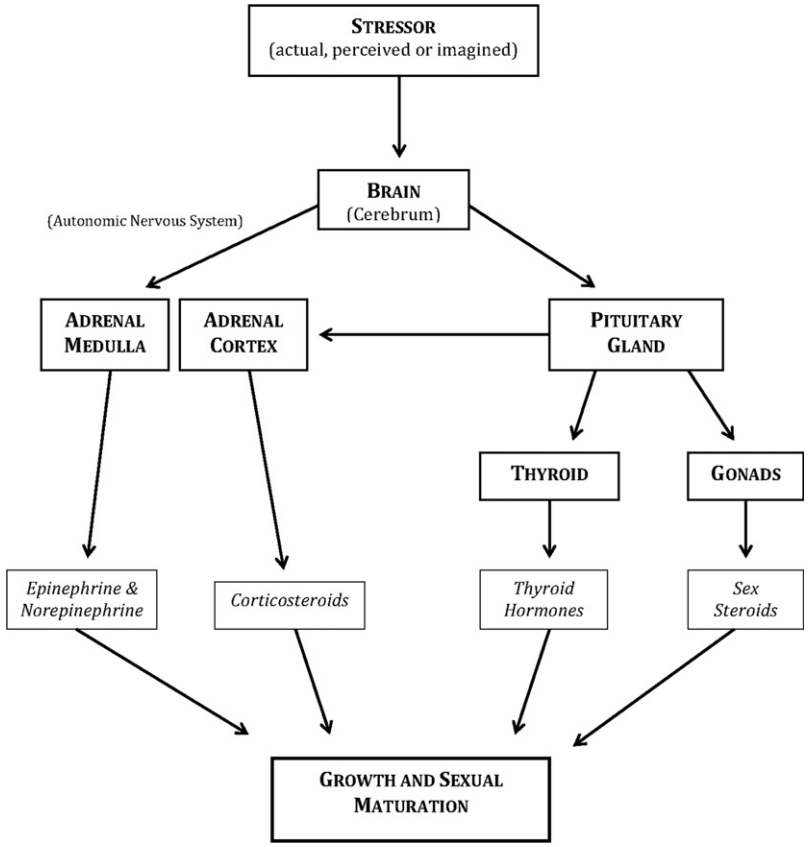

Figure 10.4 The biological stress response.

One general observation is that the effects of any pollutant depend on the dose. Effects of noise are not present in any study unless the exposures are quite high, perhaps over 100 dBA. Statements summarizing the relationship between noise and growth have to be careful about specifying the range of exposure observed. In general, statements about the relationship between any environmental factor, whether it is altitude or noise, should refer only to the ranges of exposures observed and should not extrapolate results to exposures above or below that range, otherwise results among studies will appear more inconsistent than they really are.

10.7 HOW DO WE INTERPRET DIFFERENCES IN GROWTH RELATED TO ENVIRONMENTAL FACTORS?

Recalling the two interpretations of growth reductions reviewed at the chapter's outset, it seems that the interpretation used depends on the environmental factor considered: slow and/or reduced growth is a disadvantage created by adverse health conditions (this is

the growth monitoring or "biomedical" model), or slow and/or reduced growth is an adaptive response (i.e. beneficial) to features of the environment (the adaptation model). While there is no covering law to dictate which interpretation is appropriate in which circumstances, in general, it seems that growth reductions related to anthropogenic factors (lack of material resources for the child, including poor medical care and poor nutrition) tend to be interpreted with the growth monitoring model, while growth reductions related to features of the physical environment tend to be interpreted in an adaptive framework. This distinction is not foolproof. Air pollution, an anthropogenic factor, is also a product of volcanoes and other natural processes. Ultimately, the view that growth reductions do have adaptive benefits for the individual (affecting reproduction, or functioning such as cognition) will be determined by studies that seek to measure the adaptive benefits. In general, growth alterations may be seen as the result of trade-offs between resources for growth, reproduction or survival.

10.8 CONCLUSION

In addition to effects of nutrition and socioeconomic factors, the immediate physical environment can affect human physical growth and development. This conclusion is supported by many of the studies reviewed here on altitude, temperature and climate. Studies of pollutants also show effects on growth, although many of these studies have flaws that come from valued and important limitations on experiments with people. However, the results from numerous, carefully executed studies of non-human animals support the studies on humans. When compared to the effect of malnutrition, the effect of pollutants can seem small, but the size of the effect depends on the extent of exposure to the pollutant. If we clean up the environment, child growth will be little affected by air pollution, but if children grow up in an environment with many types of pollution, the effect of all the pollutants together may be large. Indeed, studies show that in industrialized countries the poor children have more exposure to pollutants, and the result can be impaired growth. It is wise to remember that exposure to many of the pollutants that affect growth are mediated by social factors, as is nutritional deprivation. Thus, growth can be considered as a monitor of the general quality of children's environments.

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SUGGESTED READING

High Altitude

Frisancho (1993)[25] is a classic introduction to high altitude adaptation, and Hall and Guyton (2011)[26] gives biomedical background on the physiology of respiration. Lampl (2005)[45] outlines theoretical debates over prenatal growth. Beall (2000)[77] is an excellent comparison of Andean and Tibetan adaptation. The quarterly journal High Altitude Medicine and Biology, available online, offers periodic reviews of problems confronting high-altitude populations or visitors.

Sleep

These articles are excellent examples of recent research:

Iglowstein I, et al. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics* 2003;**111**:302–7.
Van Cauter E, Spiegel K. Circadian and sleep control of hormonal secretions. In: Turek FW, Zee PC, editors. *Regulation of sleep and circadian rhythms.* New York: Marcel Dekker; 1999. p. 397–425.

Pollution

The journal Environmental Health Perspectives is a good source regarding pollution and health. For a review of polychlorinated biphenyls and health see:

Carpenter DO. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. *Rev Environ Health* 2006;**21**:1–23.

For a recent review of pollution and human biology see any of these:

Schell LM. Industrial pollutants and human evolution. In: Muehlenbein MP, editor. *Human evolutionary biology.* Cambridge: Cambridge University Press; 2011. p. 566–80.
Schell LM, Burnitz KK, Lathrop PW. Pollution and human biology. *Ann Hum Biol* 2011;**3**:347–66.
Schell LM. In: Mascie-Taylor N, Yasukouchi A, Ulijaszek S, editors. *Human variation: from the laboratory to the field, Series. Impact of pollution on physiological systems: taking science from the laboratory to the field*, vol. 48. London: Taylor and Francis; 2010. p. 131–41.

INTERNET RESOURCES

Toxic substances and health: http://www.atsdr.cdc.gov/
Specific toxicants: http://www.atsdr.cdc.gov/toxprofiles/index.asp
Toxicants and the environment, including some information on human health effects: http://www.epa.gov/
Noise pollution: http://www.nonoise.org/
Sleep: http://www.sleepfoundation.org/
High altitude: http://www.altitude.org