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Feature Article

Developmental Adaptation: Where We Go from Here

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ABSTRACT The concept of developmental adaptation is a powerful framework that can be used for understanding the origin of population differences in phenotypic and genotypic biological traits. There is great deal of information describing how developmental responses can shape adult biological outcomes. Specifically, current research suggest that individuals developing in stressful environments such as high altitude will attain an adult enlarged residual lung volume that contribute to the successful cardiovascular adaptation of the high-altitude Andean native. Likewise, studies on the etiology of the metabolic syndrome indicate that development under poor nutritional environments elicit efficient physiological and metabolic responses for the utilization of nutrients and energy, which become disadvantageous when the adult environmental conditions provide abundant access to food and low energy expenditure. Epigenetic research in experimental animals and retrospective research in humans confirm that environmental influences during developmental period have profound consequences on the phenotypic expression of biological and behavioral traits during adulthood. Research on epigenetics is a productive direction for human biologists concerned with understanding the origins of human biological variability. Am. J. Hum. Biol. 21:694–703, 2009.

The term adaptation is used in the broad generic sense of functional adaptation, and it is applied to all levels of biological organization from individuals to populations. A basic premise of this approach is that adaptation is a process whereby the organism has attained a beneficial adjustment to the environment (Baker, 1966; Baker and Weiner, 1966; Dubos, 1965; Frisancho, 1975, 1993; Lasker, 1969; Lewontin, 1957; Mayr, 1999; Mazess, 1975; Proser, 1964). This adjustment can be either temporary or permanent, acquired either through short-term or lifetime processes, and may involve physiological, structural, behavioral, or cultural changes aimed at improving the organism's functional performance in the face of environmental stresses. If environmental stresses are conducive to differential mortality and fertility, then adaptive changes may become established in the population through changes in genetic composition and thus attain a level of genetic adaptation. In this context, functional adaptation, along with cultural and genetic adaptation, is viewed as part of a continuum in an adaptive process that enables individuals and populations to maintain both internal and external environmental homeostasis. Therefore, the concept of adaptation is applicable to all levels of biological organization from unicellular organisms to the largest mammals and from individuals to populations. This broad use of the concept of adaptation is justified not only in theory but also because it is currently applied to all areas of human endeavor so that no discipline can claim priority or exclusivity in the use of the term (Dubos, 1965). Functional adaptation involves changes in organ system function, histology, morphology, biochemical composition, anatomical relationships, and body composition, either independently or integrated in the organism as a whole.

The concept of developmental adaptation examines how organisms develop and aims to provide an integrated framework for investigating development in its ecological context providing an integrated approach for investigating the origins of adult phenotypic and genotypic variability. In the 1970s I postulated the hypothesis of developmental adaptation to explain the enlarged lung volume and enhanced aerobic capacity that characterize the Andean high-altitude natives. According to the developmental adaptation hypothesis "adult biological traits are the result of the effects of the environment and the physiological responses that the organism makes during the developmental state" (Frisancho, 1970, 1975, 1977). This concept is based upon the fact that the organism's plasticity and susceptibility to environmental influence are inversely related to developmental states of the organism so that the younger the individual the greater is the influence of the environment and the greater the organism's plasticity (Frisancho, 1975, 1977, 1993). Hence, variability in physiological traits can be traced to the developmental history of the individual (Fig. 1). Current investigations demonstrated that environmental events might disrupt developmental processes leading to positive or negative outcomes. It appears that the extent to which the developmental pathways may be altered by environmental events depends on sensitive periods in development. Specifically two paradigms are evident:

1. The effect of environmental factors on phenotypic traits is inversely related to the developmental state of the organism: the younger the organism is, the greater the influence.
2. The adaptability of the organism to respond to the effect of environmental factors is inversely related to the developmental state of the organism: the younger the organism is, the more adaptable it is. Hence, adult phenotypes might be different or similar depending on the interaction of regulatory mechanism operating during development and particular environments.

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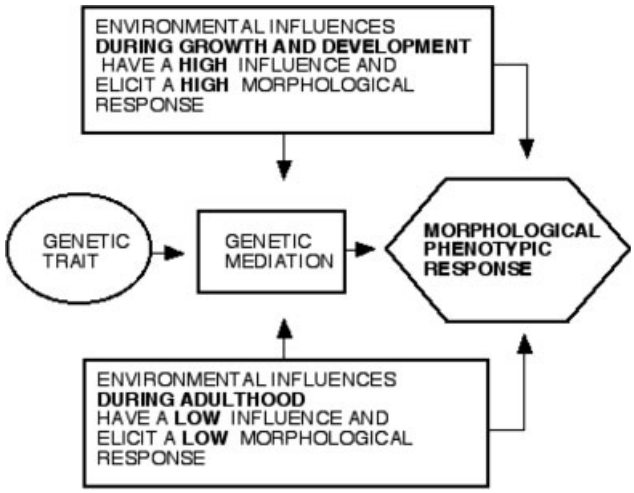

Fig. 1. Schematization of developmental adaptation and genetic mediated by environmentally induced epigenetic responses environment and the phenotypic morphological outcome.

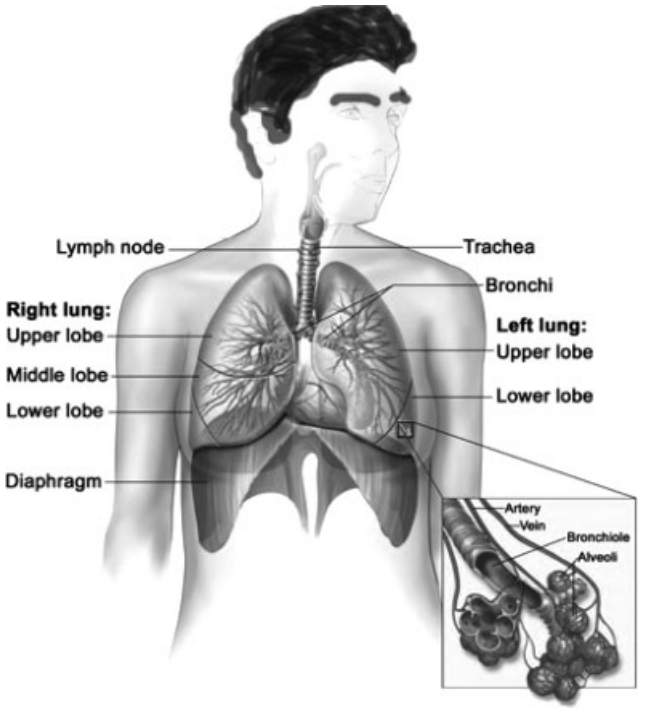

Fig. 2. Anatomy of the lung. The lungs are divided into small segments terminating into small alveolar sacs called alveoli, whose function is to uptake oxygen and release carbon dioxide to be exhaled. (Modified by the author from http://cancerinfo.tri-kobe.org/for_patient/pdq/summary/EN/CDR0000062956.html.)

Currently, the concept of developmental adaptation has been applied to explain the variability in adult behavioral traits such as learning and crime and delinquency (Kruger et al., 2008; Sroufe et al., 2005; Yueh-Au Chien, 1994) in sensory inputs and auditory spatial processing (Martin and Martin, 2002), tolerance to surgical intervention (Faury et al., 2003), and variability in oxygen consumption and mitochondrial membrane potential in energy metabolism of rat cortical neurons (Schuchmann et al., 2005), and variability in increased risk of adult obesity and cardiovascular problems associated with the metabolic syndrome (Barker, 1994). A common denominator of all these studies is that humans and many other organisms are conditioned by experiences during development and as developmental experiences are important contributors to variability in adult phenotypic behavioral and biological traits.

In this review I will summarize the evidence supporting the applicability of the concept of developmental adaptation to account for the increased lung volume of Andean high-altitude natives and the origins of the high risk of the adult metabolic syndrome incorporating information derived from thrifty gene, thrifty phenotype, and epigenetics.

LUNG FUNCTION AND THE ORIGIN OF ENLARGED LUNG VOLUME OF THEANDEAN HIGH-ALTITUDE NATIVES

Developmental plasticity of the anatomy and function of the lung

Lung function at sea level. The lung is the most essential respiration organ whose principal function is to bring oxygen into the body and to remove carbon dioxide and release it from the bloodstream into the atmosphere. The millions of small thin-walled air sacs called alveoli accomplish this exchange of gases. Air after entering the nose or mouth, travels down the trachea, which divides into one left and one right bronchi. The lung consists of two lungs located in the chest on either side of the heart. Each lung is divided into lobes, with three lobes on the right and two on the left. The lobes are further divided into lobules, and thin-walled alveolar sacs that are made up of clusters of alveoli. The left bronchus leads to the left lung and the right bronchus leads to the right lung. This bronchus continues to divide into smaller and smaller bronchioles. The bronchioles are connected to the alveoli (Fig. 2).

Alveoli. The alveoli consist of small porous membrane pockets whose major function is the uptake of oxygen and release of carbon dioxide (Fig. 2). The lungs contain about 480 million alveoli. Deoxygenated blood from the heart is pumped through the pulmonary artery to the lungs, where through a network of fine capillaries oxygen diffuses into blood and is exchanged for carbon dioxide in the hemoglobin. The oxygen-rich blood returns to the heart via the pulmonary veins to be pumped back into systemic circulation.

The inspiration and expulsion of air named ventilation is driven by muscular action of the diaphragm and the internal intercostal muscles, which increase and reduce volume of air in the lungs. By increasing volume and thus decreasing pressure, air flows into the airways down a pressure gradient, and by reducing volume and increasing pressure air flows out from the airways up to a pressure gradient.

Lung function tests

Lung function tests are traditionally done through spirometer. Spirometric permits the measurement of the amount (volume) using a device called a spirometer. The lung volume is divided into several volumes, among which the most common are the forced vital capacity (FVC) and residual volume (RV) (Figs. 3 and 4).

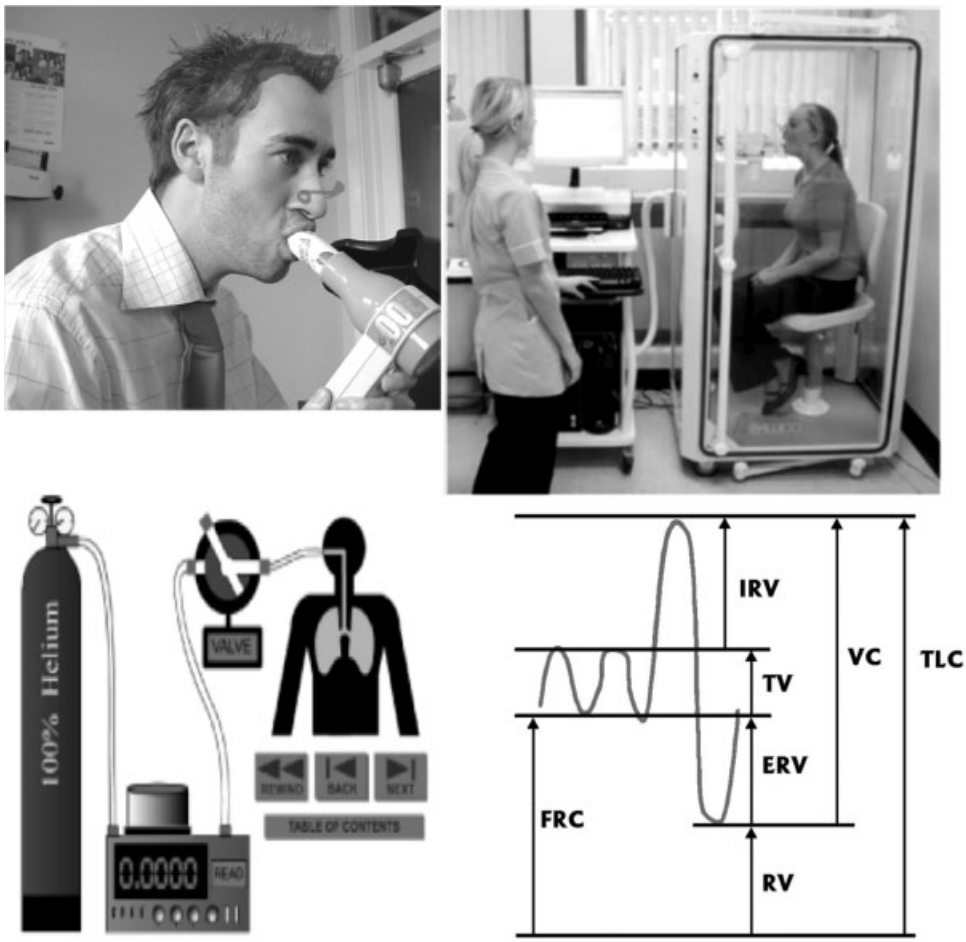

Fig. 3. Lung function tests through measurements of lung volumes. The forced vital capacity (FVC or VC) can be measured with portable spirometer (top left), while the residual volume (RV) can be measured via plethysmography (top right) or with helium (bottom), which provide the components of total lung volume (TLC) (Adapted from Frisancho, 2006).

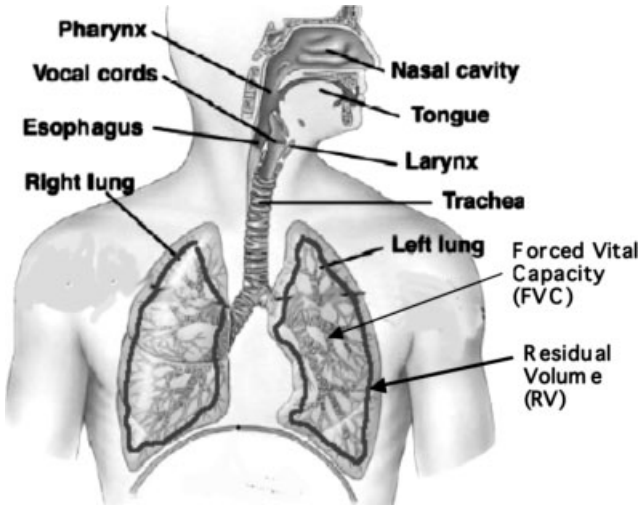

Fig. 4. The respiratory system showing the areas of the lung measured with forced vital capacity (FVC) and residual volume (RV) of the lung. (Adapted from Frisancho, 2006).

Forced vital capacity (FVC)

The FVC is the volume of air in the lung that can be exhaled during a forced maximal expiration following maximal inspiration of air. At sea level usually averages about 3–4 l in women and 4–5 l for men. The volume varies with height and age. The forced vital capacity is measured through spirometry (American Thoracic Society, 1991; Hankinson et al., 1999). A spirometry test is performed using a device called a spirometer, which comes in several different varieties. The basic FVC test varies slightly depending on the equipment used. The procedure includes asking the participant to take the deepest breath they can, and then exhale into the sensor as hard as possible, for as long as possible. The highest value of three measurements is recorded as the FVC. During the test, soft nose clips are used to prevent air escaping through the nose. In addition to the FVC most spirometers provide information of the volume of air expired in 1 second (FEV1) and 3 seconds (FEV3), and the ration of FEV1/FVC, which provide information about lung obstruction (an FEV1/FVC $<70\%$ is indicative of lung obstruction).

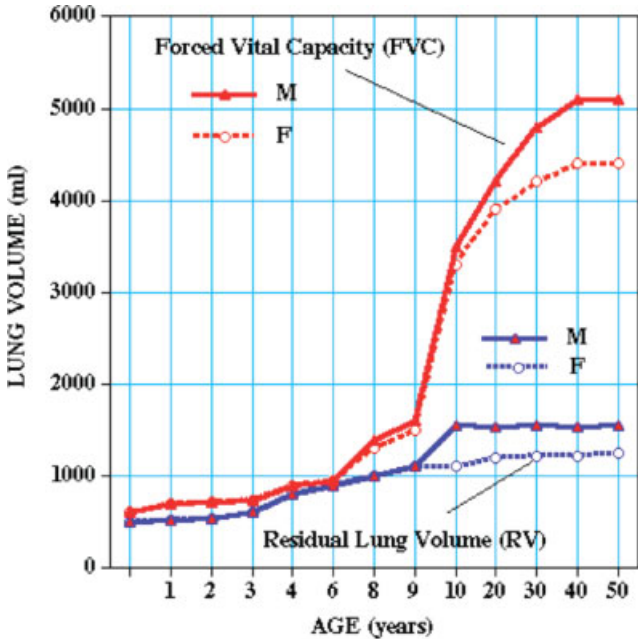

Fig. 5. Allometric growth of lung volumes. The forced vital capacity (FVC) continues to change through the life cycle continuing to grow through both childhood, adolescence, adulthood, and decline with aging. In contrast the residual volume grows mostly during childhood and early adolescence. (Derived from Frisancho, 1993). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

Residual lung volume (RV) and alveolar area

Residual lung volume (RV) represents the amount of air in the alveolar areas of the lung. The RV averages about 0.8–1 l for women and 1–1.5 l for men. The volume varies with height and age, level of physical activity during childhood, and exposure to high altitude during childhood. Residual lung volume is usually measured by nitrogen dilution or helium method. In the nitrogen dilution method (Frisancho et al., 1973; Wilmore, 1969), the participant is connected to a 7-l espirometer filled with 5 l of oxygen and take four to five fairly deep respirations. After inhaling the air from the respirometer the participants are instructed to breath deeply outside air and exhale maximally. At the end of the maximal inspiration the participant breaths air from the respirometer and a sample of alveolar air is obtained. The inspired and expired air and in the respirometer is analyzed for its nitrogen percentage using a continuous electronic gas analyzer. The residual volume is obtained by computation as the difference between the initial volume of oxygen in spirometer and the expired air, percentage nitrogen in the expired air and inspired alveolar air. In the helium dilution method (Frisancho et al., 1997), the participant breath and rebreaths into spirometer filled with 600 ml of helium, 2 l of ambient air, and 1.5 l of 100% oxygen. Once all the gas concentrations are stabilized the functional residual capacity (FRC) is derived calculated as the percent difference between the initial concentration of helium in the spirometer and concentration of helium at the various points in the rebreathing period. Residual volume is calculated as the difference between the expiratory reserve volume and functional residual capacity. In both methods all the measurements are corrected for atmospheric temperature and pressure saturation (ATPS) and body temperature saturation (BTPS).

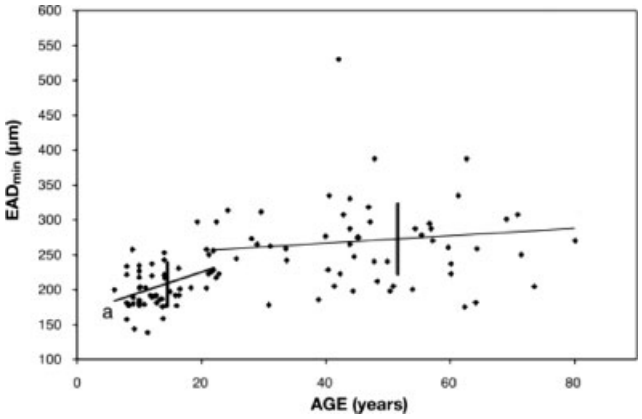

Fig. 6. Alveolar Area. As measured by the Effective Air Space Dimensions (EADmin) in vivo, increase rapidly until the age of 8 years, and thereafter with few exceptions, remain nearly constant through age 80. (Adapted from Zeman and Bennett, 2005).

Alveolar area. Animal postmortem studies found a direct relationship between the number of alveoli and residual lung volume (Burri and Weibel, 1971 a,b; Yilmaz et al., 2007; Zeman and Bennett, 2005). These studies determined that although there are about 480 million alveoli in the residual volume the number of alveoli varies with the size of the RV and it can range from 274 to 790 million. The alveoli have a thin membrane that provides the vital surface for gas exchange between the lungs and the blood. The alveolar area is highly vascularized, where millions of short thin-walled capillaries lie side by side with air moving on one side and blood on the other (Fig. 2). Diffusion of oxygen and carbon dioxide occurs through these capillaries. During each minute at rest approximately 250 ml of oxygen leave the alveoli and enter the blood and about 200 ml of carbon dioxide diffuse from the blood into the alveoli to be exhaled. Thus, the alveolar area and hence the residual volume of the lung plays an important function in supply of oxygen and getting rid of carbon dioxide. Hence, the bigger the alveolar area the greater is the capacity to pickup O_2.

Allometric growth of the lung compartments at sea level

Forced vital capacity. The forced vital capacity grows during both childhood and adulthood (Figs. 5 and 6). It can increase from 1 l of vital capacity during childhood to about 5 l by adult and decline with aging reflecting the changing aerobic needs of the organism (Janssens et al., 1999). For example, exposure to conditions that decreases oxygen availability as it occurs with high altitude results in enlargement of the forced vital capacity. Likewise, clinical removal of one lung results in some compensatory enlargement of the remaining lung (Mineo et al., 2004; Verpeut et al., 2000). Similarly, becoming involved in continuous physical activity during adulthood can expand the vital capacity by as much as 20% when compared with

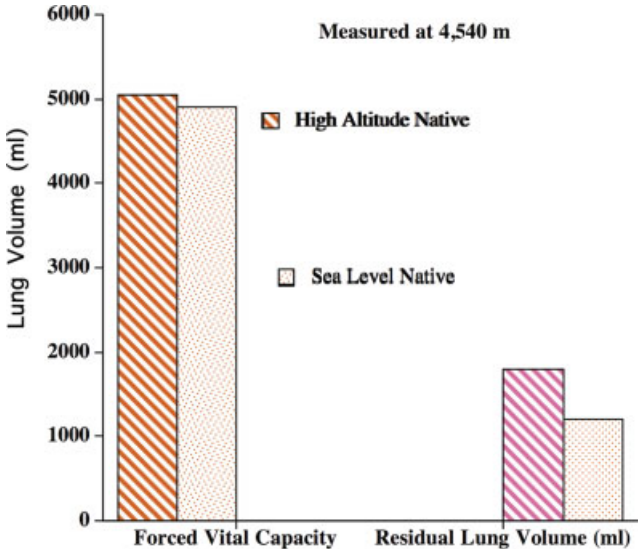

Fig. 7. Comparison of lung volumes (measured by forced vital capacity and residual lung volume of male subjects born and raised at sea level and those born and raised at high altitude and measured in Peru. (Based on data from Hurtado, 1964). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

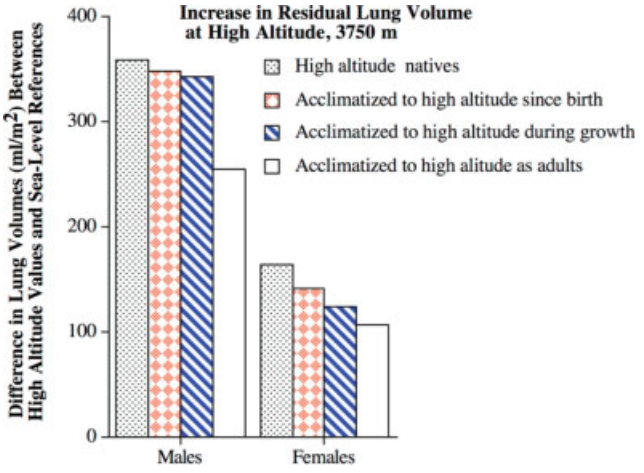

Fig. 8. Development of altitude-associated increase in residual lung volume in La Paz, Bolivia, situated at mean altitude of 3,750 m (12,375 ft). Among high-altitude natives, sea level subjects of foreign ancestry acclimatized to high altitude since birth, during growth and during adulthood. (Data from Frisancho et al., 1997). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

sedentary individuals (Cheng et al., 2003; Fuster et al., 2008).

Residual lung volume. The residual lung volume grows mostly through childhood (Fig. 5). Spirometric studies indicate that on the average the residual lung volume attains it mature value by the age 10 years (Polgar, 1979).

Alveolar area. The growth of the alveoli is limited by the developmental stage of the organism. Some investigators based on autopsy studies report that "There was little or no increase in the total number of alveoli after the age of 2 years" (Thurlbeck, 1982) and others based of in vivo studies of children indicate that from childhood (age of 6 years) to adulthood a constant number of respiratory units is maintained (Zeman and Bennett, 2005). As illustrated in Figure 6, with few exceptions, at the end of 8 years of age the children establishes the number of alveoli.

In summary, the growth of the lung volumes is allometric. The residual lung volume is characterized by a rapid growth during childhood and slow growth during adulthood. In contrast, the forced vital capacity grows continuously during both childhood and adulthood, but without increase in alveolar cell proliferation. The fact that the alveolar area plays an important function in the supply of oxygen and the excretion of carbon dioxide the growth of the residual lung volume has profound implications for the functional adaptability to high altitude.

Developmental adaptation of the lung at high altitude

As shown in Figure 7, a unique feature of high-altitude Andean natives is the enlarged residual lung volume (Hurtado, 1964). Determining the origin of the enlarged residual lung volume has been a major concern in studies of human adaptation.

Humans. Comparison of the lung volumes of sea level subjects of foreign ancestry acclimatized to high altitude (La Paz, Bolivia situated at mean altitude of 3,750 m (12,375 ft) indicate that, compared with that expected at sea level, those acclimatized since birth or during growth showed a similar increase in residual lung volume as the high-altitude (urban) natives) (Frisancho et al., 1997) (Fig. 8). In contrast, those acclimatized to high altitude as adults exhibited smaller increases in residual lung volume. These findings suggest that acclimatization to high altitude during development (that is, since birth or during growth) is an important component for the increased residual lung volume that characterizes high-altitude natives (Brody et al., 1977; Hurtado, 1964). Recent studies conducted among Peruvian subjects born and raised at sea level and born and raised at high altitude demonstrates that the attainment of lung volume (measured by FVC) is strongly influenced by birthplace, emphasizing the importance of developmental adaptation to high altitude (Brutsaert et al., 2004).

Experimental studies. Various studies have demonstrated that young rats and beagles (Bartlett, 1972; Bartlett and Remmers, 1971; Burri and Weibel, 1971 a,b; Cunningham et al., 1974; Johnson et al., 1985), after prolonged exposure to high-altitude hypoxia (>3,100 m), exhibited an accelerated proliferation of alveolar units and accelerated growth in alveolar surface area and lung volume. In contrast, adult rats, after prolonged exposure to high-altitude hypoxia, did not show changes in quantity of alveoli and lung volume (Bartlett and Remmers, 1971; Cunningham et al., 1974; Johnson et al., 1985). The increase in size of gas exchange units was evenly distributed between alveoli and ducts in young animals but involved alveolar ducts

more than alveoli in adult animals. In other words, in immature rats lung growth was hyperplasic with regard to functional units but in adult animals reflecting a limited potential for cell proliferation at the alveolar level lung growth was hypertrophic. In terms of gas exchange was hyperplasic growth is more efficient than hypertrophic growth. Studies of foxhounds demonstrate that the developmental adaptation induced by high-altitude residence (3,800 m) from 2.5 to 7.5 months of age improves enhances lung diffusing capacity for oxygen that persists at least 2.5 years after returned to sea level (Hsia et al., 2007; McDonough et al., 2006). In other words, adaptations acquired during development at high altitude do not regress after return to SL, thereby contributing to long-term enhancement of long-term lung function and oxygen transport during adulthood at sea level.

In summary, both experimental studies on animals and comparative human studies of samples residing at high altitudes indicate that the attainment of a large residual lung volume at high altitude requires exposure to high altitude during the period of growth and development. Since the residual volume plays a major role in the oxygen uptake the fact that is attained before adulthood illustrates that the adult lung volumes are determined by the developmental factors. The enlarged residual lung volume or large alveolar area because its role on the supply of oxygen and the excretion of carbon dioxide contributes to the normal aerobic capacity that characterize high-altitude natives (Brutsaert et al., 2004; Frisancho et al., 1995; Hurtado, 1964).

DEVELOPMENTAL ADAPTATION AND THE METABOLIC SYNDROME

The metabolic syndrome is an increasingly common disorder in industrialized countries. It is a condition characterized by a cluster of traits including insulin resistance, high cholesterol, and excess weight that increase the risk for developing coronary heart disease, stroke, and diabetes (see Alberti et al., 2006; NCEP, 2001; WHO, 1999 for alternative definitions of the metabolic syndrome). To account for the increased frequency of the metabolic syndrome in modern population three research paradigms such as the "thrifty" gene hypothesis, "thrifty phenotype" or "fetal" programming hypothesis, and the epigenetics hypothesis have been advanced, which will be summarized below.

The thrifty genotype

Neel and colleagues (Neel, 1962; Neel et al., 1998) attempted to explain the epidemic proportions of diabetes in Native American populations such as the Pima Native Americans by postulating the existence of a "thrifty gene" that increased the risk of Type II diabetes. According to this hypothesis, the basic defect in diabetes mellitus was a quick insulin trigger. Insulin's main function is to assist in the homeostasis of glucose in the blood. Specifically, when blood glucose levels are too high, the pancreas releases insulin to increase tissue uptake of glucose to reduce blood levels. Conversely, when blood glucose levels are low the organism secretes glucagon and growth hormone, which in turn, induces the release of stored glucose and fatty acids into the blood stream raising serum glucose levels. The insulin response is to activate an uptake of glucose into the muscle cells for storage and in liver cells it influences the conversion of glucose to fatty acids for storage in fat (adipose) tissue. This response was asset during times of abundance because it would allow an individual to build up energy reserves more quickly and thus better survive at times of food scarcity. Under these conditions the thrifty gene was selected to regulate efficient intake and utilization of fuel stores. In other words, during periods of food storage and famine, those with the thrifty genotype would have a selective advantage because they relied on larger, previously stored energy to maintain homeostasis, whereas those without "thrifty" genotypes would be at a disadvantage and less likely to survive and reproduce. However, under modern conditions of abundant food, and sedentary lifestyle, this genotype becomes perversely disadvantageous. With a constant abundance of food, insulin levels remain high, resulting in tissues becoming less sensitive to the effects of insulin. This reduced sensitivity in the effects of insulin results in chronically elevated blood glucose levels—Type II diabetes—and related chronic health problems (e.g., obesity).

A test of the genetic predisposition to Type II diabetes involved a comparative study of the Pima Indians of Southern Arizona and the Pima Indians of the Sierra Madre mountains of Northern Mexico (Knowler et al., 1990; Price et al., 1992). These two groups, which were separated about 700 to 1,000 years ago, differ in their life style. The Arizona Pima live under conditions with access to a high-fat, highly-refined diet, and low-energy expenditure. In contrast, the Mexican Pima still pursue a much more traditional lifestyle and diet based on occasional intake of lamb and poultry and mainly on beans, corn, and potatoes, grown by traditional and physically very energy demanding techniques. These two groups differ significantly in the frequency of obesity and diabetes. The Arizona Pima adults have a body mass index (BMI) of 33.4 kg/m^2 compared with a BMI of 24.9 kg/m^2 in the Mexican Pima (Ravussin et al., 1994). Likewise, in the Arizona Pima 37% of men and 54% of women were diabetic while only 2 of 19 women and 1 of 16 men were diabetic (Knowler et al., 1990; Price et al., 1992). In other words, although the Mexican Pima share the thrifty gene with Arizona Pima their increased frequency of obesity and diabetes is more evidence that an abundance of fatty foods and modern sedentary lifestyles are the real culprits. Thus, it is not the presence of a "thrifty gene" alone that results in increased rates of diabetes, but rather the interaction of "thrifty metabolism" with modern dietary and lifestyle conditions that results in increased rates of chronic health problems.

In summary, the thrifty genotype hypothesis has been used to explain the endemic levels of obesity and diabetes among nonwestern populations such as South Pacific Islanders, Sub-Saharan Africans, Native Americans in the Southwestern United States, Inuit, Australian aborigines, etc. (Eaton et al., 1988; O'Dea, 1991) newly introduced to industrialized diets and environments. In contrast, the thrifty gene hypothesis is not applicable to populations that have not subjected to periodic famines such as Europeans.

The thrifty phenotype

Recently, Barker and associates (Barker, 1994; Barker et al., 1989; Hales and Barker, 1992) have reported an

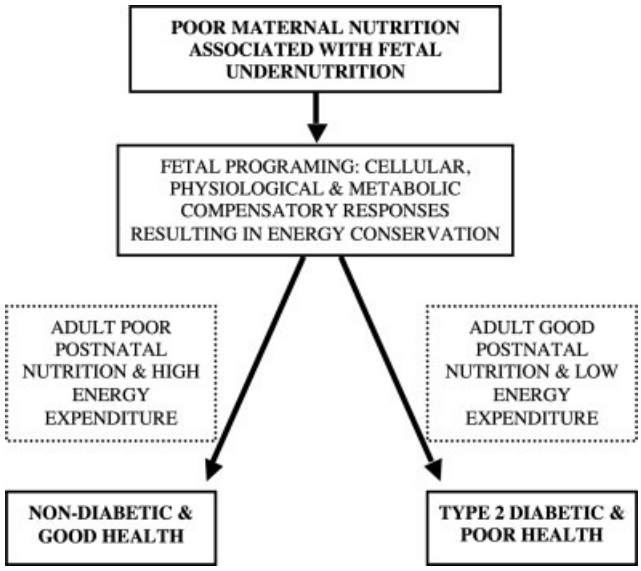

Fig. 9. Thrifty phenotype. The risk of diabetes Type II and metabolic syndrome in adulthood is associated with prenatal undernutrition resulting in efficient physiological adaptation that becomes detrimental when food is abundant and energy expenditure is low.

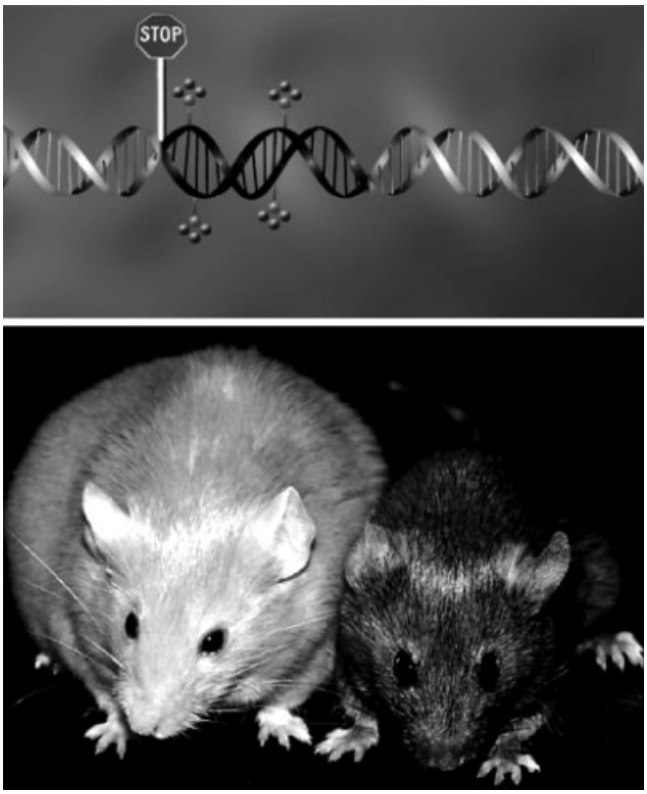

Fig. 10. DNA methylation of genetically identical twin agouti mice that possess different coat colors. The additions of a methyl group (−CH3) to fifth position of cytosine (top) modifies the CpG islands from signaling molecules and prevent the expression of the dark coat color (lower right) resulting in yellow (lower left) coat color. (Adapted from http://www.niehs.nih.gov/research/supported/programs/envepi/index.cfm).

inverse relationship between birth weight and the risk of hypertension, cardiovascular disease, and Type II diabetes in adulthood when the individual is well nourished postnatally. To account for these observations Barker et al. proposed that adverse effects in utero induce cellular, physiological, and metabolic compensatory responses such as insulin resistance, high blood plasma levels of fatty acids, which result in energy conservation and reduced somatic growth that enable the fetus to survive undernutrition. This response is referred to as the thrifty phenotype hypothesis (Armitage et al., 2005). These responses that were adaptive under poor prenatal conditions become a problem if food becomes abundant. In this view, thrifty physiological mechanisms are adaptive in poor nutritional environments but in rich environments are maladaptive. That is, what was positive under reduced availability of nutrients particularly during periods of rapid development becomes negative in rich environments, because it facilitates nutrient absorption and hence increased risk of adult obesity and the suite of risk factors for cardiovascular disease known as the metabolic syndrome (Fig. 9).

In summary, it appears that nutrition and other environmental factors during prenatal and early postnatal development influence cellular plasticity, thereby altering susceptibility to adult cardiovascular disease, Type II diabetes, obesity, and other chronic diseases referred as the adult metabolic syndrome. The finding supports this hypothesis that the offspring of women who were starved and become pregnant during the Dutch famine of World War II were found to have impaired glucose tolerance and increased adiposity in adulthood (Stein et al., 1975, 2007).

Epigenetics and diet

Waddington (1942) introduced the term epigenetics to describe the causal interactions between genes and environmental events, which influence the phenotype expression. It specifically, refers to the transmission of phenotypic traits from one generation to the next that do not depend on differences in DNA sequence (Holliday, 2006; Jablonka, 2004). During the last two decades, there has been an accumulation of observations indicating that the expression of DNA traits can be affected by environmental factors acting during development. Specifically, experimental studies showed that identical-twin mice differ in the color of fur one has brown fur and will grow up to be lean and healthy while the other has yellow fur and becomes obese and prone to cardiovascular disease (Fig. 10a).

The different phenotypes are due to a process known as methylation, which refers to the alteration of the genetic environment through the addition of a methyl group (−CH3) to fifth position of cytosine, which is largely confined to CpG dinucleotides (Fig. 10b). This addition by modifying the CpG islands prevents signaling molecules from reaching to the promotor site to turn the gene on and prevent the expression of the dark coat color. In other words, methylation shuts off the gene that controls dark fur color and allows the yellow color to be expressed. Thus, the process of methylation works as a kind epigenome that dictates which genes in the genome are turned on and which are not, a process that can differentiate even between identical twins.

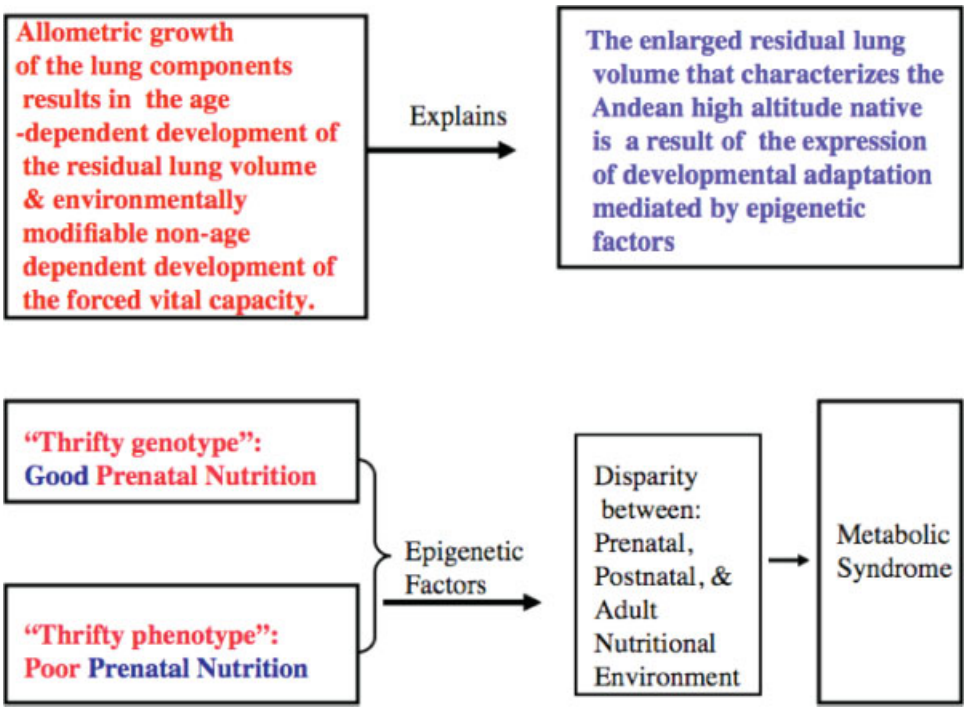

Fig. 11. Schematization of the process of developmental adaptation and its role in the attainment of enlarged lung volume of high altitude natives and the metabolic syndrome. Adaptations acquired during the developmental period are important components for the enlarged residual lung volume that characterize Andean high-altitude native. Likewise, diet-induced changes in "epigenetic programming" during fetal and postnatal development may precipitate the metabolic syndrome. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

Recently, experimental studies indicate that bisphenol A (BPA) can alter gene expression and affect adult phenotype by modifying CpG methylation at critical epigenetically labile genomic regions (Waterland and Jirtle, 2004). Bisphenol A is used in the production of polycarbonate and plastic containers and in the organism acts like the body's own hormones. Thus, there is concern that long-term exposure to bisphenol A may induce chronic toxicity in humans (vom Saal and Hughes, 2005). Fortunately, the effects of methylation are not permanent but reversible as shown by the fact the yellow agouti (Avy) whose diet was supplemented with folic acid, vitamin B-12, choline, betaine, and zinc that counteracts the DNA methylation and changed the coat color from yellow to dark brown coat (Dolinoy and Jirtle, 2008), which is associated with low risk of cardiovascular disease. However, the reversibility of altered DNA methylation defects takes places when the intervention is done early in development (Pogribny et al., 2006).

Current research indicates that diet can influence the degree of methylation by changing the availability of folate, choline, and methionine (Ross and Milner, 2007) Experimental studies found that dietary methyl deficiency (of folate, choline, and methionine) in a rat model altered hepatic DNA methylation patterns and induce hepatocarcinogenesis in the absence of a carcinogen (Poirier, 1994). Animal studies found that changes in methionine metabolism increased homocysteine production, which led to changes in DNA methylation in the fetus liver (Rees, 2000). Since homocysteine is associated with increased risk of glucose intolerance and hypertension it has been postulated that an increase in homocysteine during fetal development might contribute to glucose intolerance and hypertension in adult life (Ross and Milner, 2007). A recent study reported that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–1945, six decades later, had less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings (Heijmans et al., 2008). Likewise, first-trimester prenatal exposure to famine appears to be associated with addiction problem (i.e. alcohol and drug abuse) later in life (Franzek et al., 2008).

Transgenerational epigenetic effects

It has been suggested that the epigenetic modifications brought about by parental conditions may be expressed even in grandchildren. Extensive records of a population in Overkalix cohorts, northern Sweden found an association of the grandparental prepubertal slow growth periods (SGP) or rapid growth periods (RGP) and parental periods of low or high food availability with grandchildren mortality and disease risk (Kaati et al., 2007). If the SGP of the grandparent was a period of high food availability then grandchild may had reduced longevity but an increased mortality. The extent to which these associations represent multigenerational epigenetic effects is unwarranted, because in part ruling out genetic and societal confounders and in the absence of molecular evidence is extremely difficult. Hence, future research must be focused on long-

term transgenerational studies whereby many birth cohorts are studied using intensive prenatal and perinatal genotyping across generations. Only then variability in the expression of phenotypic traits can be attributed to epigenetic changes.

In summary, epigenetic effects exist that are not necessarily adaptive and in many of these cases the inherited phenotype is actually detrimental to the organism. Environmental exposure to nutritional, chemical, and physical factors can alter gene expression, and affect adult phenotype a process known as epigenetics. In all these studies, the extent of DNA methylation depends on and is inversely related to the developmental state of the organism so that the younger the greater are the epigenetic marks, including CpG methylation than in mature ones. These studies together support the hypothesis that early life environmental conditions such as nutrition and other environmental stimuli can cause epigenetic changes in humans that persist throughout life and modify the adult phenotypic biological as well as behavioral traits. Considering society's increased concern about environmental pollutants this area of research should be an important future direction for human biologists.

OVERVIEW

The concept of developmental adaptation has become a major focus for studying the origins of human diversity (Frisancho, 2006). The applicability of this research strategy is based upon the premise that human biological responses to environmental stress represent a continuous process whereby past adaptations are modified and developed to permit the organism to function and maintain equilibrium within the environment to which it is daily exposed. As schematized in Figure 11, applying the developmental conceptual framework adaptations acquired during the developmental period are important components for the enlarged residual lung volume that characterize Andean high-altitude natives. From the studies of the thrifty genotype and thrifty phenotype and its relationship to the etiology of metabolic syndrome it is evident that what was positive under reduced availability of nutrients particularly during periods of rapid prenatal development becomes negative in rich environments. The evidence suggests that diet-induced changes in "epigenetic programming" during fetal and postnatal development may precipitate the metabolic syndrome.

Given the increasing concern about the proliferation of balanced and unbalanced diets research in epigenetics may provide the bridge between the thrifty genotype and thrifty phenotype to unravel the interrelations of the impact of early diet might help how the organism adapts to a given environmental condition that differs in nutritional resources resulting in the diverse phenotypic expression of physiology, body size, and health risk of contemporary and past human populations. Human biologists doing research in epigenetics may bridge both the thrifty genotype and thrifty phenotype hypotheses and provide a link between genes and the environment concerning disease predisposition to metabolic syndrome and its associated diseases. Hence, epigenetics is a productive research direction for human biologists concerned with understanding the origins of human biological variability.

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