

Perinatal origin of adult diseases

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ABSTRACT

Three relevant, interrelated scientific advances are described: the concept of critical periods (CPs), the Barker Hypothesis (BH), and the underlying epigenetic mechanisms involved. Critical periods are genetically programmed, highly sensitive time intervals during which the interaction between environment and individuals generates the development of physiological processes related to physical growth and development, survival (breastfeeding), social behavior, and learning. Barker hypothesis is based on the finding that prenatal malnutrition (for example, low birthweight) is closely related to mortality due to cardiovascular disease (CVD) in the adult, and to the risk conditions leading to it: insuline resistance, metabolic syndrome, obesity, and high blood pressure. This association is not due to genetical causes, but secondary to nutritional deficits which in turn generate epigenetic mechanisms of methylation of DNA basis and cromatine proteines (histones), which do not modify the genetic code but modulate its expression, reinforcing some genes, inhibiting others, regulating when and where they are expressed. These genes participate in the process called programming, consisting of permanent changes in the response to stimulation of metabolic and hormone regulators, such as, for example, increasing insuline resistance. Epigenetic changes persist even when original conditions (fetal or perinatal malnutrition) are no longer present. This, in turn, affects health of the offspring later in adult life, creating thus the same environmental prenatal conditions to the next generation. This transgenerational effects of early nutritional experiences are more frequent in population groups of low socioeconomic level, and consequently have serious implications in the future health of Latin American populations. **Keywords:** cardiovascular disease, fetal malnutrition, low birth weight, metabolic syndrome, epigenetics.

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INTRODUCTION

In the last decades, major advances have been made in the knowledge of consequences that some early health experiences have in adult life, especially those occurring in the perinatal period. The advances

described in this article are: 1) the discovery of critical periods, 2) the late effects of nutritional and psychosocial injuries during the perinatal period, and 3) the underlying epigenetic mechanisms. These three advances are closely related; for this reason, I describe them in this article with the purpose of reinforcing the bridges of knowledge between pediatrics and adult medicine.

Critical periods

In 1973, Konrad Lorenz, an Austrian ethologist, won the Nobel Prize in Physiology or Medicine for studying the behavior of some birds, including geese. One of his most important experiments consisted in exploring why geese walked, and even swam, in a straight line. He discovered that geese were genetically programmed so that in the first hour after hatching out of the egg, the baby goose established an attachment with the first living being it saw. Logically, this was the mother goose and, when this occurred, the baby goose would walk behind her for the rest of its life (see Figures 1 and 2).

The experiment consisted basically in replacing the presence of the mother goose with the investigator at the time the egg hatched and Lorenz obtained the expected results: the baby geese walked in a straight line behind him, as shown in Figure 3, while the mother goose was left out of the picture, unaware of the drama.¹

Based on this concept, Lorenz described something that biologists (and also Sigmund Freud) had been working on: the concept of the *critical period*, during which certain environmental stimuli caused an indelible imprint that irreversibly determined the future behavior of an individual in relation to a specific being (mother, child, etc.).²

Many examples can be seen in the field of ethology. If a newborn calf is taken away from the mother cow for a week immediately after birth and is bottle-fed in a house away from its mother, once returned to the field, it will be incapable of following the herd because it will not have established an attachment with other animals of its own species in the critical period of the first days of life.^{3,4}

If a lamb is put next to an ewe that has just given birth, it will be accepted for breastfeeding as long as it occurs in the first hours after birth. However, if a newborn lamb is taken to an ewe two days after the birth, it will accept neither that lamb nor any other. The critical period for sheep to create an attachment to their babies is present immediately after birth, thus making breastfeeding possible.⁴

Dogs appear to have two critical periods. The first one occurs in the first two weeks and is related to attachment and breastfeeding. The second period is somewhat variable but it usually occurs between the fourth and eighth week of life and is related to socialization, i.e., the dog will recognize as familiar (friendly, not harmful) any species seen by it during this period, including humans.^{3,4}

What happens with humans?. Studies in our species are harder because, in addition to a biological programming core that may be considered *robotic*, our behavior is modulated by a very complex level of psychological integration and an even more complex level of social integration.

The work of Klaus and Kennel in 1971 describes studies conducted in mothers who

started skin-to-skin contact in the first hour after birth and during several days after this period. A few months later, it was observed that these mothers breastfed for a longer period and, when asked how their babies were doing, they answered using more positive adjectives (cute, sweet, loving) than those whose newborn infants had been taken to the nursery immediately after birth. The authors also told the story of an event that occurred at a maternity ward in Israel where two newborn infants were accidentally switched and given to the mother of the other baby. After 15 days, when the error was discovered, both mothers showed resistance to receiving her own baby and giving back the one they had breastfed for two weeks.⁵

Valuable reviews were made on critical periods related to life preservation, behavior,

FIGURE 1. Mother goose and its babies



Source: <https://vigocanes.blogspot.com/2010/11/konrad-lorenz-y-la-impronta.html> (accessed on: September 20th, 2018).
Geese walking in a straight line following their mother.

FIGURE 2. Mother goose waiting for eggs to hatch



Source: https://www.google.com.ar/search?q=ganso+huevo&tbm=isch&source=iu&ictx=1&fir=LC1CBUBZcYxe_M%252CILRund9O61PPNM%252 (accessed on: September 20th, 2018).

When the egg hatches, the first thing the baby goose sees is its mother.

FIGURE 3. Konrad Lorenz, leading the row of baby geese



Source: Konrad Z. Lorenz. Picture by Thomas D. Mcavoy/ The LIFE Picture Collection/Getty Images). doi:<https://gettyimages.com/licence/50347572>. (Accessed on: September 20th, 2018).

The picture shows Konrad Lorenz walking and followed by a row of baby geese.

and socialization.³ Here I will describe examples of purely biological aspects.

Biologists are well-versed in the critical period of gastrulation of certain fish, during which a change in the salinity of the environment where eggs develop results in one-eyed fish.⁶

In humans, most organs have a critical period during the prenatal stage. In the case of prenatal nutritional deficit, the organism gives priority to the development of the brain and the heart, at the expense of other organs. For example, for the production of renal glomeruli, the critical period ends approximately at 34 weeks of postconceptional age.⁷ In case of a severe nutritional deficit that interferes with glomerular development, the baby will be born with a decreased number of functioning glomeruli. This leads to a relative increase in the filtered load, an increase in the glomerular filtration rate and a consequent increase work (protein load to be filtered) during the entire postnatal life,⁸ which causes a *hyperflow kidney*, with the resulting damage to functioning glomeruli. In the long term, this leads to fibrosis, then to glomerular hyalinosis, glomerulosclerosis, and, finally, arterial hypertension in adulthood.⁹

Human neurons multiply in the prenatal period, with neural replication peak at around the 20th week of gestational age.¹⁰ Before birth, babies already have the total number of neurons they will have for the rest of their lives. However, glial cells multiply up to the end of the second year of life. Certain embryonic lesions that take place in the critical period of neural replication interfere with such replication and result in an irreversible decrease in the definite number of neurons, making it impossible to recover from the lesion that affected brain development. This is what happens in the embryos who, for example, suffer maternal alcohol abuse (fetal alcohol syndrome) or congenital rubella syndrome.¹¹

In the cases described above, the critical period corresponds to the neural replication period, but other critical periods also take place in the central nervous system (CNS). One occurs during synaptogenesis and the subsequent synaptic pruning, which takes place in postnatal life. The information provided by a positron emission tomography (PET) scan has helped to learn a lot about synapses development and neural functioning during development. In the first years of postnatal life, the generation of new synapses (connections between the axon of one neuron and the dendrite of another) progresses

geometrically. At birth, the baby's brain has approximately 50 000 000 synapses; by 1 year old, there are already 100 000 000 000 synapses, and the number keeps increasing at a fast pace. But not all these synapses will remain active; towards puberty, any synapse that remains unused or that does not receive or transmit electrical stimuli will break down, axons will retract, and the synapse will disappear. Moreover, if there is no neuronal stimulus or afference for some time, neurons will die due of apoptosis.¹²

There is a critical period for the maintenance of the optical path, which goes from the retina to the calcarine sulcus, and is related to synaptogenesis. This period occurs in the first weeks of postnatal life. To remain functionally active, the optical path needs to receive, during this period, a nerve impulse from the retina induced by a light stimulus. If the optical path fails to receive nerve impulses during several weeks, synapses break down permanently and irreversibly, and babies develop amblyopia. This is what happens in newborn infants with bilateral congenital cataracts, which prevents the optical path from receiving any light. In this situation, a timely surgery to remove both lenses is critical.¹³

Figure 4 shows the reduction in visual acuity based on the time elapsed since birth up to bilateral cataract surgery, which permits the generation of a nerve impulse in the optical path based on retinal light stimulus.

One of many studies indicates that if the newborn infant is operated on before 5 weeks old, visual acuity will be practically normal, but any delay in surgery will increase the probability of a lower visual acuity, to the point that if a child undergoes surgery at 1 year old, his/her visual acuity will be 20/400. The sooner the surgery is done, the better the visual acuity will be. Therefore, it is very important to know the critical periods of certain processes during infant development.

Although regression line *B* shows a continuous decreasing trend, if the line is broken into two sections (line *A*), two trends may be observed: one is almost horizontal, which indicates that if the surgery is done in the first five weeks, visual acuity will remain normal. After this cut-off point, visual acuity starts decreasing.^{13,14}

Any ear surgeon knows that a Cochlear implant should be placed ideally before 18 months old because any delay after this age will cause greater difficulties in normal language development. If the implant is placed after 7 years

old, it will be practically impossible for the child to develop symbolic language.¹⁵

There are also critical periods for the development of a language center for a specific language. Fluency in a foreign language depends on the age at which a person starts learning that language. The earlier they start, the better their fluency will be. And this is because the level of brain plasticity varies with age. The difficulty to learn to speak a foreign language *without an accent* after 20 years old is probably due to the fact that synaptic pruning has already occurred and got rid of synapses that allow to pronounce the typical phonemes of such language.

Critical periods exist in all live beings. Those that modulate biological phenomena are related to physical growth and development. Some of the underlying mechanisms are well known, such as the periods for neural replication or the critical periods related to synaptogenesis and the subsequent synaptic pruning mentioned above. However, other mechanisms are little known, as is the case of the critical periods related to attachment, socialization, and behavior. Some authors prefer to call these *sensitive periods* because, in many cases, the consequences of any lesion occurred during these periods are not *all or nothing*, but show some level of elasticity or plasticity in terms of long-term consequences.¹⁶

However, an important biological mechanism has been discovered relatively recently. It occurs in the prenatal period and has consequences in adult health.

The Barker hypothesis

In 1989, in the county of Hertfordshire (United Kingdom), Barker observed that adults who had a weight of 12.3 kg or more at 1 year of age had a lower mortality rate than those who had a weight of less than 8.2 kg.^{17,18} He concluded that poor growth and nutrition in the first year of life were associated with poor adult health. This information was deepened and reinforced when he studied the birth weight of adults who died due to a cardiovascular condition and compared it to the birth weight of adults who died due to a different cause (tumors, accidents, etc.), and found what is shown in *Table 1*. Mortality tends to increase as birth weight lowers. A lower birth weight increases mortality from cardiovascular disease (CVD), although mortality from other causes is not modified. Barker concluded that malnutrition during the perinatal period was associated with a higher risk for CVD in adulthood.¹⁹

After these ground-breaking studies, dozens of investigations were carried out (cross-sectional, longitudinal, retrospective, prospective studies) that confirmed and deepened this hypothesis and found an association between a low birth weight (and also a low weight in the first year of life) and adult conditions that resulted in CVD: central obesity,²⁰ insulin resistance and diabetes,^{21,22} hypercholesterolemia,²³ arterial hypertension,²⁴ and a high risk for CVD.^{25,26}

Prenatal nutritional risk factors may interact with postnatal ones, resulting in a mutual

FIGURE 4. Residual visual acuity based on age at bilateral congenital cataract surgery*



* Diagram based on the one from reference 13.

After 5 weeks old, there is a risk for permanent deficit in visual acuity.

strengthening or weakening. For example, a rapid weight gain in the first months of life is also associated with metabolic syndrome and late obesity, and the combination of a low birth weight with a rapid weight gain in the first months of life is reinforced and strongly associated with metabolic syndrome in adulthood.²⁷

Not only a low birth weight and a rapid weight gain in the first year of life are associated with CVD. Even with a normal birth weight, the severe stress suffered by pregnant woman (even before pregnancy) may be associated with metabolic disorder in adulthood. The placenta contains substances capable of neutralizing a certain amount of steroids, but severe, chronic maternal stress may cause the release of a large amount of steroids, which is in turn associated with a higher incidence of adult metabolic syndrome.^{28,29}

In addition to low birth weight, low weight, and a rapid weight gain in the first year of life, there is a fourth risk factor based on an auxological-physiological phenomenon identified by Rolland-Cachera: *adiposity rebound*. As shown in Figure 5, in physiological conditions, during the first months of life, the baby experiences a large increase in skinfold thickness (both tricipital and subscapular skinfolds), which peaks around 9 months old. After this time, the skinfold thickness reduces progressively until approximately 4-5 years old, and from this point, children experience a new rise in adipose tissue called *rebound*. A very early rebound, as shown for two children in Figure 5, is associated with adult obesity and metabolic syndrome.³⁰

The figure shows the average (schematic) curve of the tricipital skinfold thickness (in mm) in males. It is worth noting the remarkable adiposity increase in the first months of life, which decreases after the first year. Approximately

at six years old (*f* arrow), adiposity rises. Some children (like those shown in curve *a*, solid line, and *b*, dotted line) *rebound* earlier than the average curve. These children also have a higher risk for CVD in adulthood.³⁰

The risk for CVD is not only associated with early malnutrition, a rapid weight gain in the first year of life, and an early adiposity rebound; in population studies, it has been associated with adverse life conditions during childhood, such as poor socioeconomic or unfavorable housing conditions.³¹ In terms of population, these findings are compatible with the results commented above.

For this reason, Barker insisted that the underlying causes of the association between CVD and living conditions (poverty, substandard housing, etc.) should be looked for in the direct relation between CVD and birth weight and nutritional and perinatal growth conditions.¹⁸

A low birth weight has another important effect on a child's development: its impact on physical maturation. Children with a low weight or with a rapid weight gain in the first year of life have a greater risk for obesity during school age,³² higher levels of central adiposity,³³ and also an accelerated skeletal maturation.^{34,35} A rapid weight gain in the first year of life and an accelerated skeletal maturation may be signs of a trend towards obesity and metabolic syndrome, besides indicating that the individual is moving faster towards adulthood.

There is an underlying endocrine condition that supports the relation between low birth weight and metabolic syndrome. Children with a low birth weight have a greater insulin resistance, beta cell dysfunction (a trend associated with exaggerated adrenarche), and reduced sex hormone transport proteins.³⁶⁻³⁸ Such endocrine picture, together with high insulin-like growth factor-1 (IGF1) and aromatase levels, may induce gonadotropin-releasing hormone (GHRH) pulse generation, which would explain the findings of Adair et al., who described an early menarche in girls with a low birth weight.³⁹

After reviewing the relevant studies in this subject matter, the association between a low birth weight and the risk for adult CVD may be characterized as follows:

- It is not genetic. In monozygotic twins (with exactly the same genetic composition) with a different birth weight, the one with the lower weight has a higher risk for CVD than the one with a higher weight at birth.⁴⁰

TABLE 1. Mortality (based on cause categories) by birth weight*

Birth weight (£)	CVD**	Other causes
< 5.5	119	118
6.5	95	99
7.5	105	101
8.5	82	110
> 8.5	74	127

* Table taken from Barker (reference 17).

£: pounds.

It shows that mortality tends to increase as birth weight lowers.

**CVD = cardiovascular disease.

- The relation is independent from socioeconomic status (it is observed in all socioeconomic strata).
- It is independent from maternal smoking during pregnancy.
- It occurs in all countries of the world.
- It is related to poverty.
- It is independent from lifestyles, but some may reinforce the risk (such as sedentary habits, obesity, smoking).

Programming

It is necessary to better understand that the biological mechanisms accounting for this late effect of nutritional experiences or early psychosocial stress on adult diseases, not only are they related to CVD, but also to other degenerative diseases.⁴¹ Based on the characteristics mentioned above, it may be assumed that both problems (prenatal deficiencies and adult CVD) are connected by a gene or group of genes that act on a common product that may influence both factors (birth weight and prevalence of CVD). For example, insulin acts on glucose metabolism, but also intervenes in fetal growth regulation. However, there is increasing evidence that this is not the mechanism. At least one relevant mechanism has been identified:

programming,⁴² which consists in modifications in the response to stimulation by metabolic and hormonal regulators. For example, fetal malnutrition causes changes in insulin response, so more insulin is required to produce the same effect, i.e., insulin resistance is developed.³⁷

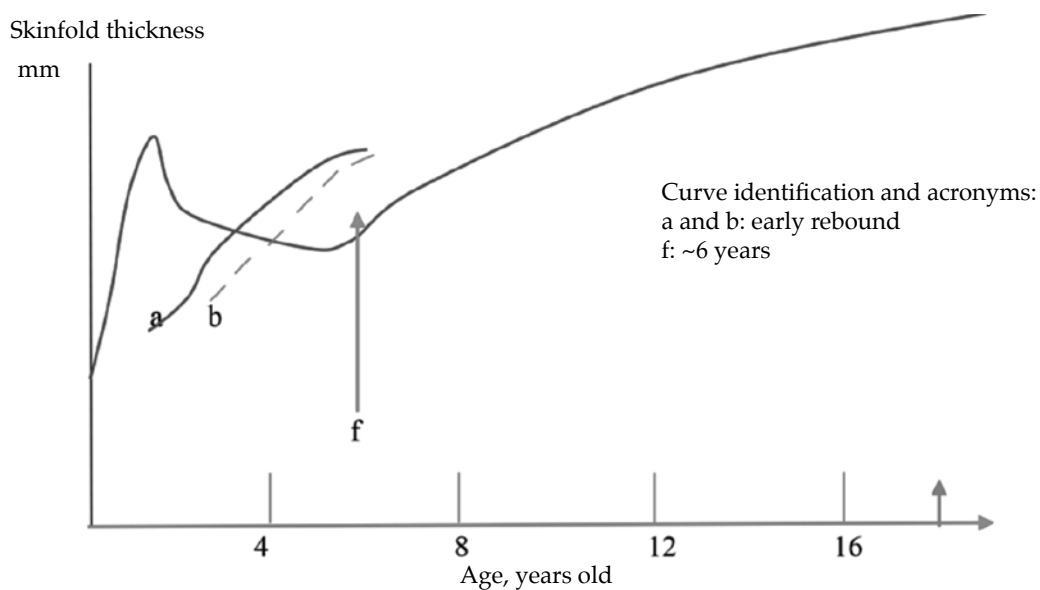
Epigenetic changes

Such *programming* or change in the response of hormonal or metabolic receptors is secondary to chemical changes occurring in the deoxyribonucleic acid (DNA) of the offspring resulting from nutritional deficiencies and other lesions. Although such chemical changes do not alter DNA base sequence (and, therefore, the genetic code), they do alter the *expression* of such code, either silencing or activating genes and defining how and when they are expressed, for example, by modifying the affinity of hormonal receptors.

Such chemical changes are called *epigenetic changes* and basically consist in the adhesion of four substances to DNA base sequences or associated proteins (histones) (Figure 6):

- Methylation (combination of bases with methyl radicals). For example, a methyl radical is attached to an adenine molecule but the position of adenine in the base sequence is not altered.

FIGURE 5. Model curve of tricipital skinfold thickness increase in males, with two individual curves that are examples of early rebound*



* This is a schematic drawing developed by the author and does not represent exact values of a child's skinfold.

- Acetylation (combination of bases with acetyl radicals).
- Ubiquitination (combination of bases or histones with ubiquitin, a protein associated with protein degradation).
- Phosphorylation (combination of bases with phosphate radicals).

In physiological conditions, DNA purine or pyrimidine bases normally have certain amount of associated methyl groups, and epigenetic changes may result in either methyl radical increase or reduction. Epigenetic changes occur without altering base sequence, i.e., without affecting the genetic code, and play a key role in gene expression by reinforcing or activating some, silencing others, and regulating when and how they are expressed. Such changes in gene expression may have a decisive effect on a specific metabolic response. For example, protein restriction of pregnant rats reduces the base methylation of the gene that encodes a glucocorticoid receptor (an extremely important hormone for stress) in the liver of the offspring.⁴³ Such reduced methylation results in an exaggerated metabolic response of the liver to stress.⁴⁴ In a similar model, maternal protein restriction reduces the methylation of the angiotensin receptor gene in rats' adrenal glands, which increases the gene's expression capacity; in turn, this contributes to the hypertension observed in these animals.⁴⁵

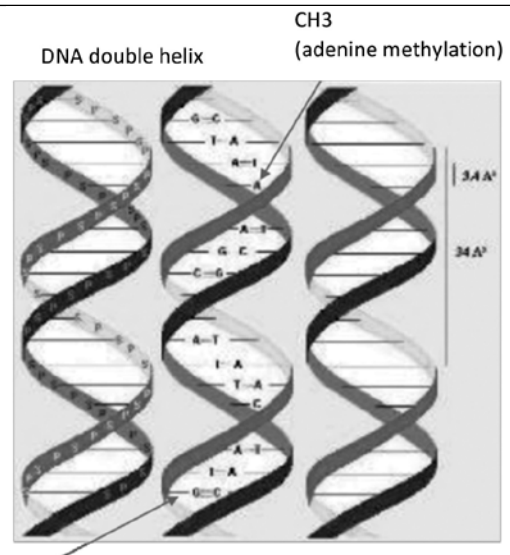
However, chemical changes of epigenetic nature have persistent consequences without the need for continuous exposure to original lesions, i.e., even when the original unfavorable conditions have disappeared. The famine suffered by the population of Amsterdam during World War II, in the 1944-1945 winter, led to the conduct of many studies on the nutritional impact of newborn infants that were gestated during a period of extreme food scarcity that deepened over time. It has been estimated that approximately 10 000 people died due to malnutrition, with an estimated average intake of 1000 calories per person at the beginning of the winter and of 500 calories towards the end. The Dutch who were exposed to severe maternal nutritional deficiencies during early gestational age suffered more health problems and obesity in their adult life;⁴⁶ however, in addition, they had a much lower methylation level in IGF-2 gene, located on chromosome 11, than in controls, *sixty years after the Amsterdam siege*.⁴⁷ Many of them then suffered the metabolic consequences of unfavorable prenatal conditions.

If any of these, such as arterial hypertension, occurs during gestation in a woman who had a low weight, such metabolic consequences may replicate in the next generation.

For this reason, it is said that epigenetic effects may have transgenerational consequences.⁴⁷ More than one generation may be required to reverse the effect of unfavorable prenatal conditions. For example, immigrants from poor countries who arrive in a new country and live in it in more favorable conditions may take more than one generation to reach an average height.^{48,49}

There are two periods in epigenetic programming: gametogenesis and early development before blastocyst implantation. The most important reprogramming takes place in gametogenesis, during germ cell production (spermatogenesis or oogenesis). After fertilization, the genome produces a methylation wave that is highly sensitive to environmental exposure: heavy metals, flavonoids, phthalates, etc.⁵⁰ In this regard, the degree of laxity in the controls of companies that spray agrochemicals in our country, increasingly closer to populations, is very dangerous to health in general, not only for those who suffer the actual agrochemical effect but also for their descendants.

FIGURE 6. Diagram of chemical changes in DNA with epigenetic consequences



CH3: a methyl radical is attached to a guanine base without modifying its position in the base sequence.

Figure obtained from <http://atlasgeneticsoncology.org/Educ/DNASpID30001SS.html> (accessed on: September 20th, 2018).

Consequences for the 21st century population

The critical period concept describes the important interaction between ethology and human growth and development science. The idea of periods highly sensitive to environmental influences, which determine behaviors and irreversible auxological-physiological phenomena that are critical for the establishment of a normal adult, sets the bases to understand human behavior and evolution.

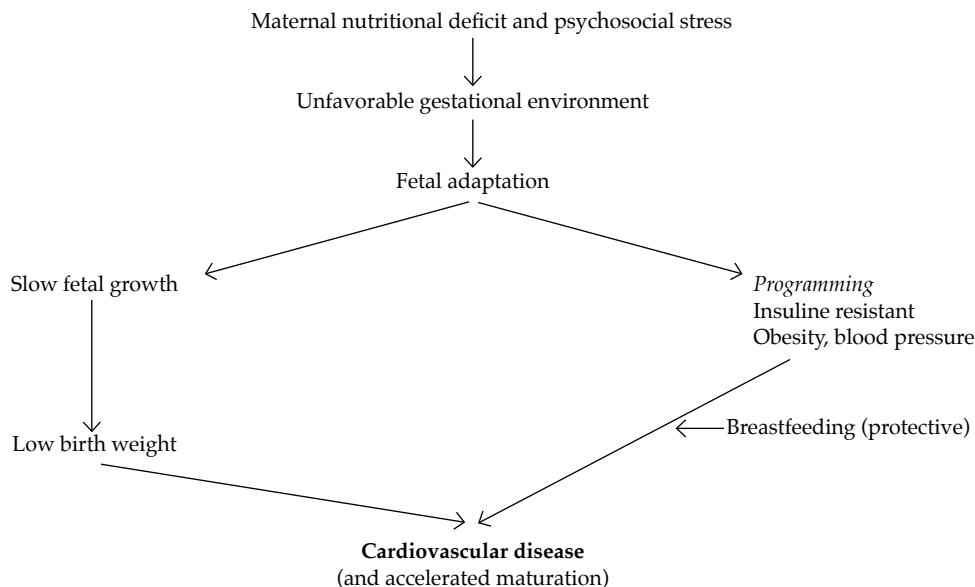
Barker hypothesis, and the scientific knowledge obtained from it in dozens of studies, opens the doors to a wide range of knowledge and understanding of the prenatal (or, even better, perinatal) origin of adult diseases. Nutritional deficiencies and other lesions responsible for stress in pregnant women that occur during the perinatal critical period are the main examples for the investigation of the childhood origin of adult diseases.⁵¹ Now it is known that lesions have an effect through the *programming* of metabolic and hormonal responses and that *programming* takes place through epigenetic changes. Here I include a diagram of the sequence of late consequences from perinatal deficits (Figure 7).

Maternal nutrition and psychosocial stressors influence the metabolic and hormonal status of the gestational environment that surrounds the developing fetus. Through *programming*, these conditions modify multiple biological

functions that increase an adult's risk for CVD. Breastfeeding is a protective factor against obesity and, therefore, CVD. The risk for CVD is also increased due to the rapid weight gain in the first year of life, and it may be reduced with breastfeeding.⁵² In turn, some biological effects of an early unfavorable environment on adults may affect the environmental health of descendants during gestation (e.g., maternal hypertension during pregnancy in association with a low birth weight in the pregnant woman), thus making unfavorable health profiles perpetual over several generations.

The adaptive nature of these mechanisms is easily understood. From a biological perspective, newborn infants from today come from the Stone Age. There have been practically no major changes in the biological composition of human beings in the past 80 000 years. In the Paleolithic setting, where food, energy, and salt were scarce, the changes described here that occur in embryos and fetuses through their pregnant mothers (*programming*) result in a strategy that allows the offspring to face such lack in postnatal life, thus maximizing adaptation in the context of environmental factors that they may eventually face during postnatal life: energy saving, insulin resistance, sodium retention, and a trend towards maintaining blood pressure. Besides, a child born in these conditions reaches physical maturation

FIGURE 7. Sequence of late consequences of perinatal deficits*



* Modified from reference 41.

faster and reproductive age earlier. Nature prepares children to reproduce as soon as possible, given the dangers of famine and stress they face. Such plasticity is mostly mediated, at least, by epigenetic changes. However, this mechanism, which may have been useful 80 000 years ago, becomes harmful in today's post-industrial society.

Effectively, these *programmable* changes in a baby born in the 21st century, with plenty of supermarkets and sodium-filled canned foods, marketing pressure that encourages the consumption of salt- and saturated-fat-rich foods, a sedentary lifestyle, and a lack of open spaces for physical activity, are a true *metabolic and hormonal error*. Human beings were prepared to live in an environment of scarce resources, eating every 48 hours, walking 15 km a day looking for food, but now they are born in a world of abundance with a sedentary lifestyle, where such *programming* easily leads them to metabolic syndrome, obesity, and CVD.

Knowing that *programming* takes place through epigenetic changes, these mechanisms have transgenerational consequences.⁵³

Many studies have confirmed the existence of a close relation between poor adult health and unfavorable socioeconomic conditions in population groups. Without underestimating the great importance of the family as an *ecological nest* that is highly determinant of a child's future, the emphasis that many pediatricians used to place on it should probably be redirected to (or complemented with) the maternal womb.

We should also probably reconsider the traditional model we have conceived of adult degenerative disease as the *result of interaction between genetic programming and an adverse environment*. Causative factors should probably include *programming* and the *specific setting of the perinatal period*.

With the marked inequality in income distribution observed worldwide at present, the unfair situation for future generations of many countries may only worsen, even more, knowing that it may take more than one generation to reverse the late consequences of unfavorable living conditions. In Latin America, including Argentina, extensive sectors are suffering these conditions, and the concepts described here are one more reason to solve inequality as a priority action of the State and thus hope for a healthier society. ■

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