



## Eugenic Therapy and the Metabolic Syndrome

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### Summary

Independent of the clinical syndrome that results in chronic inflammation, there is an overlap of the different etiopathogenic factors in the most common diseases of the modern era. Its pathogenesis also has similar pathophysiological mechanisms. Independent of the clinical syndrome that results in chronic inflammation, there is an overlap of the different etiopathogenic factors in the most common diseases of the modern era. Its pathogenesis also has similar pathophysiological mechanisms. These two facts prompt us, independent of the particular therapeutic connotations for each disease, to establish certain measures of prevention and treatment, also common, where precisely the holistic treatments that seek to Systemic homeostasis, are appropriate. These are the biological treatments, where the homo-toxicology, without a doubt, stands out as one of the best therapeutic alternatives.

The universal concept of inflammation allows us to understand more than just the symptom and going beyond a therapeutic protocol, unfortunately a lasting solution is not in our hands and may be the anthropology, sociology and ecology, the sciences involved in the definitive solutions. In the meantime, to understand that the chronic disease of the adult may have originated during gestation or before the same. We have to look at humanity in full, in its family nucleus, interacting with an environment, in a dynamic process, involutory and evolutionary at the same time, but it will be the knowledge of our own nature which will allow a better pathogenetic and therapeutic approach.

At the end of the first millennium and the start of the second a new profile in sicknesses made itself evident and it would be naive as to think that there was no epidemic relationships between the illnesses that made them up. In today's society, the analysis of each individual sickness, without taking into account the biological changes surrounding the environment in the development of modern day life, would isolate man as a strange object in his own universe and perpetuate the reductionist concept of the Cartesian medicine where the dismembering of the human body in its sickness makes an important part of its philosophy. Under the integration prism of the environmental conditions we shall analyse the epidemic variants in the prevailing illnesses. And in one medical concept we will integrate the environmental changes with the psycho, neuro, endocrine and immunological alterations of the organism, which is the origin of almost all human disease.

Keeping in mind the environmental conditions for thousands of years in the life development were relatively stable. Evolution made a permanent adjustment that allows the successful existence of life on the planet. Unfortunately, in the last few decades, human life and its relation with the stability of nature around it have changed in such a violent and extreme manner that the human being, from the biological

point of view, is not prepared to defend and crosses the information which an adverse environment supplies without suffering organic injuries. We must not forget that thousands of years in the planet can only represent one instant in genetic evolution terms. Well, the adaptive evolutionary changes are too slow as anthropology and the very evolution of life on Earth have clearly demonstrated. The result of these series of transformations is a new profile in illnesses which have never been more difficult to understand and treat and which are at this historic moment in time the first cause of humanity's morbid-mortality.

The metabolic syndrome may be the prototype most representative of modern man illnesses but other diseases such as allergies, gastrointestinal, autoimmune, psychiatric, and those that show inflammation, are not less frequent. This leads us to believe that there must be a common epidemiological basis of biological variables that allows us to have an ethipatiogenic and therapeutic approach in a universal sense which is also related. This goes beyond the analysis of a certain disease, it means to reach for the actual universal source of the disease. On the other hand, we cannot ignore the very origin of human life, going as far as the gestational period, whereas different biological factors of the woman previous to the gestation have an influence on the success of having a healthy new born, if we consider that life is one continuous interweaving of biological events that come from our ancestors and will continue until our death.

Even the pregnant woman is often just a big girl or a young woman who was recently a paediatric patient at the end of adolescence. The doctor then, not just leave a human being when it relates to their offspring. Here is the responsibility of this professional to deliver to society, a healthy woman and the obstetrician in turn to ensure a conception and a healthy life in the future. To achieve the best health conditions of a woman, before and during the design, should be the top priority for public health to ensure a healthy adult society. If the basis of the society which is childhood is healthy, the possibility that any adult society it is greater, logical question that emerges from the creation and evolution of the human being and the intervention of this in the transformation of the world. No tree, no building can be lifted as much as it is desirable, if the respective roots or foundations are faulty.

It is known that damaging factors at the start of life can be among the main causes of sicknesses which now threaten society in the different stages of life and which are a reason for the morbid-mortality rate now growing around the world. Epigenetics show us that the genetic modifications are the ultimate cause of all diseases and can be a result of unhealthy behaviour during pregnancy.

We know that the beginning of the chronic disease of the adult can be traced back to many years before they show symptoms and because modern medicine has succeeded in establishing that these may have origin in the gestation period and furthermore can have etiopathogenic factors in common with other diseases.

In my opinion, the most important organic alteration relates to the pathogenesis of all the diseases listed above, the inflammation. Therefore, the next step would be to put on the agenda the scientific truth, the biological origins of this phenomenon since the beginning of life, in other words, from the gestation. And why not in the pre-pregnant woman?

It possible that the "background" of a woman before pregnancy influences the future well-being of her offspring? Of course! Let us make a brief analysis according to some research of modern psiconeuro-endocrine-immunology.

### Interaction between Maternal Stress and Preterm Delivery

It has been suggested that it is possible to identify women who may be at risk of having a foetus of very low birth weight. A first concept suggests that there may be a genetic profile and the second that there may be a particular phenotype. The first contribution to the first theory was made by quantifying IL-8 and pro-inflammatory cytokines, which were over-expressed in patients with infections associated with preterm birth [1,2]. It seems that it is possible that a genetic polymorphism in one of these genes could produce in the mother or the foetus greater susceptibility to infection, in combination with or without psychosocial stress or other variables that could be disease producers during pregnancy.

The second contribution is related to the common polymorphism in the genes of the glucocorticoid receptors and the response to stress [3] Wust S and cols., They found healthy women with variability in the response to stress of glucocorticoid receptors to stress, depending on whether the answer to this is quantified with one or the other of the genotype of receiver. This concept opens up new possibilities to relate stress to the immune system, possibly leading to the risk of infection, (and thus increased risk of premature delivery), with or without associated polymorphism, depending on the genetic susceptibility to inflammation, the inflammation present before and during pregnancy and the allostatic overload of women. Allostatic overload is defined as the wear of the neuro-endocrine systems, for an extreme activity or too low, in response to the tensions and the need to adapt [4]. The allostatic overload quantifies the physiological and neuro-endocrinological fluctuating changes of the organism, produced by the acute and chronic psychosocial stress, over time. This allostatic overload can somehow be quantified through scales of assessment of different biological parameters, based primarily on the functioning of the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system and cardiovascular system.

The response to psychosocial stress or physical stress is different and individual from person to person. Not everyone responds similarly to one and the same situation, neither does the same stressful situation produces the same effect in all organisms. The adaptive mechanisms that seek homeostasis, called allostasis, are the same that since millions of years ago have been produced in response to stress. However, the tensions and threats of modern life generated changes that even though they may allow a reasonable efficiency in the face of stressful situations, can generate a debt, a price that sooner or later take a toll on the health of people. That is to say that each situation that puts into play homeostasis is likely to leave a residual charge, called allostatic overload, this means an imminent danger to our health. In 1988 Omer H. and Everly GS. described the emotional events that can lead to preterm delivery as "Disorders of arousal or hyperactivity of the limbic

system" [5] emphasizing mainly in the prejudice of the cumulative effect and the chronicity of stress; making us understand in this way, the importance of the different parts of the circuit of the stress in the brain, in the limbic system and the autonomic nervous system.

Recent studies have demonstrated that anxiety, depression and anger that somehow reflect the maternal stress, have an adverse impact on the foetal weight, the time of gestation and neonatal behaviour [6-8]. Without a doubt, they are important factors that could mark the psyche of the women in their first years of life, the genetic predisposition and the phenotype of the women that are prone to preterm birth [9]. Finally, Hobel Calvin J. Suggests that the allostatic overload and stress are related to the ethology of preterm or low birth weight [10] which means that the cumulative wear of neuro-endocrinological mechanisms of women, due to psychosocial stress, independent of other producers of preterm or low birth weight child, could contribute to the early termination of the pregnancy. The stress by itself seems to be the most relevant factor responsible in the pathophysiological changes of neuro endocrine and immune type, in both the foetus and the mother. The first real connection between the stress during pregnancy and the biological development in the twentieth century, was described by Sontag (1940) [11]. Sontag observed a relationship between the emotional disturbances in pregnant women and the difficulties in early feeding of the infant. He attributed these problems to prenatal development, where the foetus developed an overactive autonomic nervous system.

Although I don't know of similar modern research, a phenomenon of great epidemiological importance which meets all of the physio-pathological descriptions is the reflux of the infant and the behavioural disorders that accompany it as restlessness, sleep disorders, irritability and difficulty sleeping. After the first two years, usually become apparent another clinical picture is different, the hyperactive child syndrome (hyperactivity, aggression and attention disorders and learning). These biological alterations are exactly the research of Sontag, embodied with the modern medical nomenclature. Anderson and cols. (1941), noted that the mothers had premature births, more often than not, they were workers [12].

In 1963, Günter [13] clearly related psychosocial stress with premature delivery, until now, multiple studies have related stress with preterm and low birth weight of the child. The observed changes in the concentration of neuropeptides in pregnant women derived from the placenta are unique and play an important role that cannot be supplied by the brain. The CHR of the placenta is the neuropeptide that is used to establish communication between the placenta and the maternal and foetal adrenal glands for the production of precursors of oestrogens, which are important for the growth and uterine perfusion. The exponential increase in the CRH from the placenta has an important role on the time of delivery. Unfortunately, the activation of the expression of genes CRH, is a consistent response to maternal stress and prepares the foetus and uterus for childbirth. It has been shown this entails elevations in the quantities of CRH in the foetal circulation, in line with the maturation of the pregnancy [14,15]; suggesting that this peptide is essential for the activation of the foetal HPA axis, which is considered to be mature during the second trimester of pregnancy [16].

The sharp increase of the maternal CRH near the end of the pregnancy supports the idea that this hormone stimulates the synthesis of ACTH and foetal adrenal glands and the secretion of cortisol and dehydroepiandrosterone, an important precursor of oestrogen produced by the placenta [17]. The positive feedback (corticosteroids),

between the foetal adrenal glands and the production of CRH, provide a mechanism for an exponential increase of CRH from the placenta and oestrogen (derived from the foetal DHEA-S), two important mediators of the delivery [18]. These data suggest that the early activation of the CRH gene expression in the placenta, describes a mechanism by which premature birth can occur.

McGregor and cols [18] identified the increase in oestradiol early, approximately 3 weeks before the preterm birth. This increase usually happens at the end of pregnancy. This is an example of how the foetus and placenta indicate to the neuroendocrine system of the mother the time of delivery. The relationship between the neuroendocrine system of the mother and the CRH of the placenta and foetal HPA axis, can be a survival mechanism, which stimulates the foetal maturation and in this way, increases the chances of survival if there is a preterm birth [19].

But these endocrinological alterations produced in the preterm birth, can be the consequence and not the cause of preterm birth. That being the case, the increase of these hormones would mean that other causes induce premature labour and that this increase would only reflect an adaptive response to the threat that the nature entails in some way. It is also logical to expect that the ACTH increases early during pregnancy, in parallel with the increase of the CRH [20]. It is assumed that the origin of the ACTH is the pituitary and placenta. Wadhwa PD and cols., showed that stress during pregnancy, increases the levels of ACTH [21]. The inner layer of the adrenal gland produces catecholamines and the outer layer of the same makes cortisol and other mineralocorticoids.

The cortisol exerts a negative feedback on the CRH in the brain and on the ACTH from the pituitary gland, but in the placenta glucocorticoids stimulate the expression of genes CRH [22]; effect that is completely opposite to that produced in the hypothalamus, which suppresses the production of CRH. This difference allows the progressive increase of CRH during normal pregnancy, but can also facilitate their certain pathological conditions, such as preterm delivery, intrauterine growth retardation and pre-eclampsia [20]. The stress response mediated by glucocorticoids in the CNS, is done through the receptor type I and II. The type I plays an important role in modulating the response to the environment and the emotional stimuli, with changes in behaviour and the activity of the HPA axis [23]. The type II participates in the behaviour and neuroendocrine and autonomic response to stress [24]. During stress, it inhibits the expression of type I receptors and increases significantly the type II.

### Patho-physiology of stress

Stress can be defined as the physiological or pathophysiological way of responding to the demands of the environment. The first definition written on the concept of homeostasis was Empedocles (500-430 BC), then Hippocrates (460-375 BC) who described health as a state of harmonious balance of the elements and the disease, to the state of disharmony. In modern medicine, it was Selye (1936). Who proposed one of the most complete definitions of the pathophysiology of stress Hans Selye identified four states of reaction to stress: [23]

- Alarm reaction: characterized by sympathetic-adreno-medullar immediate download
- State of resistance: activation of the HPA axis
- General Adaptation Syndrome: adrenal hypertrophy, gastroduodenal ulceration, thymic atrophy and lymphoid
- Completeness

This brilliant concept is still in force in all its fullness within the modern psyche-neuro-endocrine-immunology. Almost no more research is needed to deduce that the chronic stress is the cause of chronic disease.

### Types of stress

The stress response, in the central nervous system is carried out in two neuroendocrine components. The CRH (corticotropin-releasing hormone)- HPA (hypothalamic-pituitary-adrenal axis) and the autonomic nervous system of the locus coeruleus-norepinephrine (LC/NE) [25] and the stress, according to its origin, it is classified in exteroceptive interoceptive. Interoceptive Stress: this refers to the neuro-endocrine-immunological information produced by an organic acute or chronic inflammation. This is the case of irritable bowel syndrome, autoimmune disease, chronic pelvic pain syndrome, infections, etc. a swollen body releasing multiple products inflammation mediators such as proteinoids, substance P, histamine, cytokines, platelet activating factor and other neuropeptides. Being a little more specific, cellular products released during the inflammation such as: (TNF)-[alpha] (tumor necrosis factor), and IL-1 and IL-6 stimulate the production of CRH and stimulate the HPA axis and the sympathetic nervous system [26].

The above mentioned substances that are released in an inflamed tissue are so important from the point of view of neuroendocrine, that modern medicine has called all of them, the tissue factor release FTLCRH (CRH).

The FTLCRH activates the central nervous system in three ways: [27]

- Through the dorsal spinal cord whose information stimulates the locus coeruleus or noradrenergic system, which in turn stimulates the stress system-level central hypothalamic releasing hormone (CRH and arginine vasopressin), with the consequences that we already know about the HPA axis.
- Directly via the bloodstream to the locus coeruleus.
- In the same way as before, in the cerebral cortex, hypothalamus and pituitary gland. In a constant feedback mechanism, once activated the central system of stress returns to stimulate the locus coeruleus, which in turn releases norepinephrine in a dense network of neurons through the brain stem, which result is an increase in the waking state and of defence, but also of anxiety.

On the other hand, implantation is an inflammatory aseptic process and is mediated by a Th1 immune response with secretion of IFN-[gamma], IL-2, and TNF-[beta], which promotes cellular immunity. If this response persists beyond the implementation, you can interrupt the pregnancy [28]. At this point, there is a change in the Th2 immune response to release other cytokines, reducing in this way, the risk of rejection. Th2 cytokines inhibit Th1 response. Usually pregnancy produces a deviation of the immune response of the Th1 to Th2, but this fact intensifies with stress. These two responses are mutually inhibitory [29]. The Th1 response stimulates the cell-mediated response: activates macrophages, the proliferation of T cells and the production of pro-inflammatory cytokines.

During stress, glucocorticoids and catecholamines inhibit Th1 response, both hormones act directly on the antigen presenting cell and on Th1 cells, inhibiting its response. In vivo studies using whole blood cultures and lipopolysaccharides, in the presence of catecholamines inhibit IL-12 production and reinforce the production

of IL-10 [30]. These changes lead to an increased risk of infections during pregnancy and therefore a greater chance of premature labour, but also greater susceptibility to allergic disease in the child.

Exteroceptive stress: Is defined as the mental stress that comes from all the emotions, this is through:

- Sensory stimuli.
- Psychic pressures
- Exogenous depression

These three concepts are basically all the daily stress to which a person could be submitted with our modern lifestyle. There are many factors, such as the sensory excess noise in the big cities, coexistence with crowds, environmental pollution, etc. Example of psychic pressure can be the one that is produced by hard work, and the very speed of our pace of life. Exogenous depression is an independent factor of the previous ones, where the affection and the emotional life of each individual plays an important role. The psycho-neuro-endocrine-immunological response to inflammation is really similar to the response to stress itself and makes an integral part of the response to stress and the link between these two situations (stress and inflammation) are its consequences. In the same way, there has been research that demonstrate how episodes of acute or chronic repeated psychological stress can induce a chronic inflammatory process and trigger various diseases of the metabolic syndrome [31].

Like the exteroceptive, interoceptive stress stimulates the CNS and produces exactly the same biological reactions in the body. Roughly speaking, the common responses produced by both stimuli, after the stimulus of the central nervous system are: [32]

- Autonomic response.
- Sensory modulation.
- Neuroendocrinological response

Autonomic response, examples: Constipation, diarrhoea, high blood pressure, sweating, nausea, adynamia, dizziness, etc.

It is believed that the mechanisms by which the physical and mental stress is associated with low birthweight and premature birth, is due to the direct action of norepinephrine on the uterine activity and its effect on the blood flow. Katz and cols., [33] conducted research that relates the maternal stress with high levels of catecholamines, they found levels as high as 58% of catecholamines in the medical women during the period of work that in periods of rest, in an intensive care unit.

In addition, these women had higher levels of these hormones as high as 64% more than women who were not working in intensive care. Gestational period of study, 26 to 37 weeks. High levels of norepinephrine and prenatal low levels of dopamine in the mother and low birth weight of the new-born, with altered levels of dopamine and neonatal serotonin, correlate proportionally with anxious mothers during the second trimester of pregnancy. The new-born children of anxious mothers showed more changes in their behaviour and lower score in the scale of analysis of the Brazelton Neonatal behaviour, whose scale analyses the motor maturity, stability and regional neurological reflexes. This study provides new information about the alterations in brain functioning of neonatal Maternal neuroendocrinological systems, for alterations.

It is important to consider not only the maternal stress in itself, but the intensity and the time it started. For example, it has been demonstrated that if the stress is introduced early in the pregnancy, the possibilities to affect the time of gestation is greater [34-37] sensory

response, examples: Dysmenorrhea, fibromyalgia, Visceral hyperalgesia, central sensitization, or trigger points mid-facial headaches, abdominal distension. We do not know how can an altered sensory response be during the pregnancy.

Neuroendocrinological Response, examples: HYPERCORTISOLEMIA, insulin resistance syndrome, syndrome of resistance to steroids or exhaustion of the pituitary-adrenal-pituitary and hypothalamic-pituitary-gonadal, hormonal disorders. It seems that the reproductive hormones released during pregnancy, decrease the response of the sympathetic nervous system and therefore decreases the possibility of an increase in blood pressure before the stress in the pregnant woman [38].

Stress during pregnancy increases the level of norepinephrine, which in turn decreases the levels of progesterone, a fact that increases the uterine irritability, predisposing to preterm birth. This fact also, automatically relates to other diseases of pregnancy to stress and inflammation. The different situations of stress, can induce a deficit of cellular immunity, which can promote bacterial colonization, vaginal discharge, and introital stenosis known as potential inducers of premature birth. On the other hand, the increase of the catecholamines induced by physical or psychological stress increases the uterine irritability and decreased placental function, which in turn decreases the production of progesterone, which also increases the uterine contractility and favours the disruption of decidual cells. These are factors that can lead to low birth weight.

### Stress factors of pregnant women

The stressors of the pregnant woman, now considered by modern medicine, are many and range from organic situations, physical, emotional and social in one way or another are generators of stress [10]. The following causes are probably the most common of stress in the pregnant woman:

#### Causes inherent in the maternal behaviour:

- Sentimental conflict with your partner.
- Personality-affective depressed, anxious or troubled, low self-esteem and psychiatric illness.
- Excess of work.
- Stressful job.
- Family conflicts of different kinds (economic, duels, bad treatment).

#### Causes inherent in the current state of health:

- Bad nutritional habits.
- Maternal malnutrition.
- Organic Disease (allergy, bowel dysfunction, metabolic syndrome, hypertension, pain, diseases of pregnancy, etc.).
- Drug addiction, smoking habit.
- Bad health system support.

#### Other:

- Low socioeconomic status.
- Low height.
- Very young or very aged.
- Short intervals between pregnancies.
- Racial issues.
- Single Mother.

It is worth emphasizing on some specific points mentioned in the list of stress-producing factors, for example, the poor nutrition of the mother may be a risk factor for preterm delivery and foetal growth retardation [39]. Pregnancy is a state of relative hypoglycaemia by the increase metabolic rate, so that the maternal organism may be less prepared to withstand stress, in conditions of poor nutrition, diet, fasting, or low caloric intake.

Malnutrition in the first quarter is associated with a shorter gestation period and malnutrition of the last quarter with a low weight, just at the moment where the woman is more vulnerable to stress. Several researches suggest that inadequate weight gain in the second quarter, correlates with a preterm delivery [40,41] and fasting during pregnancy induces an accelerated ketosis (increase of acetoacetate and beta-hydroxybutyrate and other fatty acids) [42].

Mothers with less than three meals and two snacks have a 30% higher risk of premature birth, compared with mothers who eat three meals and two or more snacks, during the day. Siega-Riz AM. And colbs [43]. found that pregnant women who fasted for a time of 13 hours or more, had higher levels of CRH and increased risk of preterm birth. It is known that high levels of CRH during pregnancy is associated with a preterm delivery [20] and the maternal stress during pregnancy is positively correlated with high levels of CRH, but negatively with the gain of the foetal weight [44,45].

Cigarette use stimulates the vigil system and therefore increases the levels of catecholamines and ACTH [46] In addition, increases the levels of catecholamines for at least 30 minutes. Therefore, the regular habit of smoking, decreases uterine blood flow [47]. In one of the investigations, the stronger marker of general anxiety related to pregnancy and childbirth was the fear and the dissatisfaction with the mothers partner [48]. This means that any risk factor before noted, could be very important and very unique for each pregnant woman, when considered individually.

### **Clinical Syndromes in the Early Stages of Life, as a Result of Inappropriate Stimulation of the HPA Axis, During Gestation**

The forerunner of ACTH is the pro-hormone proopiomelanocortin (POMC), which is synthesized in various parts of the brain and other organs such as the intestine, the reproductive organs and also the placenta [23]. The most potent agonist for the secretion of ACTH is the CHR in the anterior pituitary gland. However, during stress, the ACTH may be regulated by other peptides such as arginine vasopressin, oxytocin, angiotensin II and the intestinal peptide active vessel. The ACTH is transported by the systemic circulation to the adrenal gland, where it stimulates the synthesis of glucocorticoids, aldosterone, and androgens.

### **Could this be one of the many reasons why in the first decades of life women suffer polycystic ovary syndrome?**

It has already been demonstrated that sustained activation of the HPA axis during pregnancy, which is equivalent to the effect of physiopathologically neuro-endocrinological programming produced by any factor that causes intero or exteroceptive stress, fetal distress, preterm delivery and low birth weight, may result in incidence of metabolic disorders later in the life of the adult and is due to a prolonged stimulation of the central axis HPA, as we shall see later on. It sounds logical that a subtle but sustained stimulation of the adrenal glands

also produce an increase in androgens, that, in addition to the genetic predisposition and other factors that favour the systemic inflammation, which by itself causes activation of the shafts, this could be the ethology and the pathogenesis of this disease, that modern medicine already classified within the metabolic syndrome. The adrenal gland produces androgens in fetal life during childhood and it seems to be responsible for the formation of body hair and acne in puberty, in some women. The adrenal gland is directly stimulated by a preganglionic neuron, there is not a postganglionic neuron, as in the other thoracoabdominal sympathetic connections. Therefore, a kind of direct communication of the central nervous system stimulates the adrenal gland.

On the other hand, the effect of the catecholamines released by the gland are 5 to 10 times more powerful than those that are released in the neuronal synapses. This is due to the fact that the metabolism of these hormones is much slower in the systemic circulation. These hormones increase the vascular tone and the heart rate, so that it is utopian to think that the prolonged stimulation of the adrenal glands, secondary to an effect of programming in the uterus may be another cause of hypertension in the adult life and symptoms of dystonia neuro-vegetative, among which are the sweating, alterations in heart rate and digestive disorders. The adrenaline decreases gastric emptying and intervenes in the production of the above effects. Neither is it utopian to think that the reflux of the infant, illness that often occurs with decreased gastric emptying, have an explanation in the alterations of the central axis HPA, apart from the already known allergy or intolerance to cow's milk. The activation of the locus coeruleus-norepinephrine system leads to the release of norepinephrine in a dense network of neurons of the brain stem, which enables the states of waking and alertness. Unfortunately, an important stimulus sustained over time not only reinforces the above effects, but that produces anxiety.

An effect of fetal programming in the HPA axis that extends after the neonatal life, would also explain the behaviour of uneasiness and anxiety of the infant with reflux in its first few months and subsequently various altered states of behaviour as the hyperactive child syndrome. Acute Stress increases the adrenal gland the release of catecholamines (epinephrine and norepinephrine) and norepinephrine in the nerve terminals. But the chronic stress increases the activity of enzymes involved in the synthesis of catecholamines. This in turn leads to aging, alterations in the reproductive field, immunosuppression, and various psychic behaviours. Let us add that these children once they are born are usually spontaneous or iatrogenicity continue with an inflammatory state throughout childhood and why not, indefinitely throughout their lives. Reason enough to perpetuate the effect of fetal programming.

It seems that the effect of a neuroendocrine programming, not only can occur in the uterus, but later during childhood. For this reason, different stress factors during childhood can determine a certain vulnerability to disease later in life. It has been shown that the separation of parents during gestation or early in childhood, may have a higher risk of depression in adult life [49-51]. It is believed that stress early in life is associated with anxiety and bad temper in the adult through the CHR [52]. This hormone is also at the core of the tonsils, which seems to participate in the cognitive and emotional process and in the brain stem in the serotonergic and noradrenological tracks that are projected to the brain [53-54].

Subtle situations of stress suffered early in life, can cause alterations in the programming of the HPA axis [55]. There is a direct relationship

with the distant attitude and coldness of the mothers with their children in the early stages of life, and depression and anxiety of the same, in their adult life [56,57] and also a well-structured family appears to be associated with greater tolerance of the children to chronic stress [58,59]. We already know that depression can have similar etiopathogenic factors to stress and inflammation. Therefore, it is logical that these three components of the disease relate to one another, not only in its origins but in the pathogenesis of the disease. It has already been shown that stress and depression, produce exactly the same endocrinological alterations in the HPA axis. But the chronic inflammation can also cause the same alterations, regardless of depression and stress. The equivalent clinical trial is that the chronic depression can lead to stress and chronic inflammation, such as stress leads to depression and swelling and inflammation stress and depression, in a pathophysiological triangle that it can become a vicious circle and be the cause of the most diverse clinical syndromes in the life of the human being, at any age.

On the other hand, progesterone is a hormone that is essential for the maintenance of pregnancy and to the modulation of the immune system, its deficit favours the deviation of the immune system of Th1 to Th2 (allergies) But one of the situations that reinforce this immune system phenomenon during pregnancy, it is maternal stress [10] by integrating in this way, once more, a number of pathogenic disorders of the most common diseases of modern man, in this case, allergies, illness that often manifest early in childhood. Seeing it in this way, we can intuit that the inflammation is manifested with different clinical syndromes, depending on the age, genetic and environmental variables of the individual. In the next section, we will see the metabolic syndrome, such as late clinical manifestation of inflammation. Clinical syndromes in the medium and late stages of life as a result of inappropriate stimulation of the HPA axis during pregnancy.

## Metabolic Syndrome, Its Origin in the Beginning of Life

On a scientific basis, we have shown that there are multiple risk factors that can lead to a premature birth. An infant with low birth weight and other diseases manifest mainly in the first few years of life, where the organic or emotional stress, is the fundamental cause.

### How can we relate these events with the metabolic disease that can occur several decades later?

The pathophysiological process of stress-chronic inflammation and vice versa may be submitted at any time of the life of the human being. Let us return again to the beginnings of human life, the gestation. Women can reach the moment of it with either of the two variables (disease producing stress and/or swelling), add to the above that this woman may have an already established allostatic overload, a genetic susceptibility and a pathologic phenotype, which not only increases the likelihood of failure in pregnancy but a chronic disease in the future, if she manages to survive.

Various researchers, including Dr. David Barker have been able to establish that both the new-born babies of low birth weight for gestational age as premature babies, are most at risk of suffering or dying of one of the diseases of the metabolic syndrome, in adult life [60].

The hypotheses of D. J. P. Barker are the following:

- Many human foetuses have to adapt to a limited supply of nutrients. In fact, they permanently change its structure and metabolism.
- These changes may be the source of a number of diseases later in life, including coronary heart disease and stroke, diabetes, and hypertension.

In the foetal life, tissues and organs go through a period called "critical" in its development. These periods coincide with rapid cell divisions. The programming or the "Programming", allows to analyse if an insult or a given stimulus have lasting effect or persistent throughout life [61,62]. At the beginning of the last century, when the Japanese expanded their domains and the troops had to live in warm climates, they realized that there were significant differences in tolerance to weather or in the ability to adapt to the heat. The physiological studies showed that this fact was related to the number of sweat glands functioning [63]; people with more glands are cooled more quickly. There was no relationship with the number of glands or genetic effects.

The Japanese physiologists explored this phenomenon early on. They found that at birth all humans have the same number of sweat glands, but in none of them are functional. The explanation for this is that in the first 3 years of life, a proportion of glands become functional, according to the temperatures at which the child was exposed. Having the greatest number those who were exposed to warm climates. After this time, the programming is completed and the number of glands is established. The development of the glands encapsulates the concept of "programming". This refers to the critical period of development, where the system is plastic and sensitive to the environment and therefore can be tailored to your requirements and then follows a period where the system loses these qualities. This concept covers a number of pathological situations that the child of our time is suffering in their first years of life and that, thanks to the ability of natural adaptation, is for the most part seen in the exercise of the daily practice of medicine. One of these pathological situations to which we refer, perhaps the most representative of them, is the allergic disease in its different presentations but getting back to our main objective, which is the metabolic disorder, it is unquestionable that malnutrition is one of the most powerful influences that alter the neuroendocrine mechanisms of the organism, from foetal life and subsequently at any age.

The malnourished child in his early life is adapted with a body structure. What is new is that some of the "Memories of the body" of early malnutrition become a pathology in the adult life. The classic example is seen in our indigenous or mestizos of peasant origin, which for some reason were moved from their birth -place to the city, where they have a life completely sedentary and often improved their nutritional conditions. This particular human being in his new *modus vivendi* tends to be small in stature and obese. These two conditions reflect, the first of its origin and the second the urbanization of their customs. But beyond the particular phenotype of this character, it is the metabolic diseases that usually accompany it, like diabetes, hypercholesterolemia, hypertension.

What is worrying is that not only the first generation suffers the metabolic syndrome of immigrants, their following generations also suffer from it. For example, adult immigrants from Mexico residents in Los Angeles, USA, suffer from diabetes mellitus type II, in up to 7% of the adult population. In the African immigrant population something similar happens, Here we can integrate two different concepts, the first is that a malnourished mother is usually the peasant women (black or

indigenous) is at higher risk of having a child in the same way with a thin phenotype with low weight or premature. This individual would be part of the first-generation immigrants in the city and thrive economically while changing their habits of life in general, genetically speaking are not prepared and the consequences as we know them, in these conditions, obesity and insulin resistance syndrome is established as the most important clinical manifestations. Perhaps these humans would not suffer the same metabolic problems if they continued to live in the same environment where they were born because there is a high caloric expenditure and food intake may be deficient.

The second concept refers to the fact that these obese women have large children, precisely because of their metabolic conditions of insulin resistance. These children will suffer in their adult life the same diseases as their mothers because her insulin resistance syndrome is reduced during pregnancy the quantity and quality of the foetal beta cells of the pancreas, a fact that makes it vulnerable to a metabolic problem, type diabetes mellitus type II, in his adult life but something more ominous can happen when the foetus really suffers Intrauterine malnutrition. It has been demonstrated by experiments on animals that the conditions of malnutrition in utero, lead to changes in blood pressure, cholesterol metabolism, insulin response to glucose and other endocrine-metabolic functions, which moved to the human being, are a cause of disease. [61,64]. The human foetus adapts to malnutrition with metabolic changes and redistribution of blood flow and changes in the placental foetal production of hormones that control their growth [65].

The first change of metabolic adaptation in the foetus is the catabolism trying to steal energy from its own body [66] but a prolonged malnutrition stops its growth. This shows that the foetus can survive by reducing the use of substrate and the metabolic rate. If the damage is at the end of pregnancy, the foetus has a cephalo-body, it has already earned its final height; if it is before the third quarter, it loses weight and height, is what is known as a child of low birth weight harmonic, a fact that has clinical implications even more serious than the first.

This body decrease indirectly reflects that all the organs in proportion suffer a physical reduction. One of them is, for example, the kidney, which can reduce its size. This can affect the rest of your life, because the cellular replication of the kidney seems to not occur after birth [67,68]. The brain seems to protect itself by producing a redistribution of flow in its favour [69,70], but the cost to the different organs to the brain is quite high, due to the size of this is very large and their greater need, If the mother decreases food intake, the foetus decreases insulin and IGF-1 (insulin-like growth factors) and concentrations of glucose, this reduces the transfer of amino acids and glucose from the mother to the foetus and if it goes on this situation, there is a decrease in foetal growth [71].

### Heart Disease Coronary Artery Disease and Cerebrovascular Accident (CVA)s

Studies in England in mortality is concerned, people who were born in the early decades of the last century, reveal that the foetal distress can have an impact on coronary heart disease, By this time a usual cause of death was low weight. The rate of death in the country - was different between different regions. Was higher in some industrial parts of the north and poor rural areas of the north and west, this is almost the same as is currently happening between health conditions

of the north and the south. In this study suggests that low birth weight rates are associated with coronary disease in the adult [72].

Barker showed that people born smaller were more likely to have coronary artery disease in adulthood than those who were born early [73]. In the study of Hertfordshire, 16,000 men and women born in Hertfordshire during the years 1911 and 1930 were studied. Mortality from heart disease was greater in the high and low weight at birth [74]. In Upsala-Suiza also found an association between low birth weight and coronary disease [75]; In USA also showed the same (8000 men studied, in the American Nurses Study) [76], In the South of India the prevalence of cardiovascular disease was 18% when the birth weight was of 5.5 lb. (2.5K) and the 4% when it was 7 lb. (3.2K) [77] Studies of the Hertfordshire records and the Nurses were based only on weight at birth. Which is a crude parameter to get a clearer idea of the nutritional status of the child, In the study of Sheffield [78] when account was taken of the height, the mortality rate was higher in men than measured 18.5 inches (47cm) or less in length. (138 compared to 98).

Another study demonstrated that the weight loss was associated with coronary disease, this was measured with the radio birth weight/length. The low birth weight, especially in the child at term is associated with coronary heart disease. In the men who were thinner at birth weight index, as measured by low birth weight/length, the rate of death was two times higher than in men who had a high ponderal index of stature. In Finland the rat of death increased with the low weight of the placenta [79]. The measures that predict coronary artery disease therefore are: head circumference, weight loss, low weight, weight of the placenta. The patterns for brain injury are different. In Sheffield, Martyn, C. N. and cols. [78] showed that the mortality due to stroke was associated with low weight, but not with the thinning. An interpretation of this study is that the brain size is said to stop the growth of the body, in late gestation.

These findings suggest that the influences in the early foetal growth and the growth of the placenta, has an important effect on heart disease and stroke. It has been argued, however, that people who have a delay of growth in utero and during childhood, you can continue to be exposed to adverse effects in their childhood and adult life. And this may alter the programming. But it can be relative to the time to consider other factors such as smoking, alcohol, sedentary lifestyle, and the style of life in general. The low birth weight has also been found associated with hypertension and diabetes type II [80,81]. This factor is independent of other factors that increase the risk in the life of the adult, but at the same time, the prevalence of worsening of the glucose is higher in people with low weight, due to the fact that they become obese in adult life.

Diabetes mellitus and the worsening of glucose tolerance was higher in people who Weight 5.5 lb. at birth than in those who weighed 9.5 lb. [80]. It has also been shown that there is an association of low weight with high blood pressure. A review of 34 studies of more than 66,000 people of all ages in several countries as well prove it [82], The difference in the systolic pressure associated with 1Kg difference in weight at birth was around 3.5 mm Hg. In clinical practice, this could be a small difference if considered individually. But it is large given a general population, due to the decline of 10 mgHg corresponds to a 30% reduction in mortality [83].

The association between low birth weight and increased blood pressure is valid for babies who were small for their gestational age rather than for preterm infants [84,85]. In these studies this association

was independent of the consumption of alcohol and high body mass. However, the body mass can be important because those born small for gestational age become obese as adults.

### Blood pressure (BP)

Blood pressure has also been found to increase with the high and low weight at birth [84-86] and with small placentas [87]. An inverse relationship between the mother's blood pressure and the weight of the baby has been found and a proportional relationship between arterial pressures is clear [88].

One of the explanations of the concentrations of plasma renin activity rates in people who were born with low birth weight is that their kidneys have less neurons. Brenner and co-workers [89,90] suggest that the delay in the foetal growth leads to a reduced number of nephrons, which in turn increases the blood pressure in the glomerular capillaries and the development of glomerular sclerosis. This multiple sclerosis leads to subsequent loss of neurons and perpetuates a vicious cycle of high blood pressure and glomerular injury. The number of nephrons in the normal population varies widely from 300,000 to 1,100,000 or more [91], and the animal and human studies have shown that rates of intrauterine growth restriction is associated with a reduced number of nephrons [90]. The ultrasound studies show that low birth weight for gestational age reduces the kidney growth during a critical period of 26 to 34 weeks of gestation, reducing the size of the anterior-posterior but not the length [92].

### Endocrine changes

Studies in animals suggest that poor nutrition foetal leads to changes for the rest of his life in the HPA axis, which in turn sets adaptation mechanisms in the control of blood pressure [93,94]. A recent study conducted in children 9 years of age in Salisbury showed that those who were born with low weight for gestational age, had adrenal androgens and urinary excretion of metabolites of glucocorticoids [95], which can be a preliminary evidence that the HPA axis is scheduled in humans. The shaft, and insulin-like growth factor (IGF-1), growth hormone can also be programmed in the uterus. Children with low birth weight had higher plasma concentrations of IGF-1 [96,97]. The IGF-1 is associated with the growth of blood vessels [96], therefore may be related to the hypertension later in life.

The dynamics of large arteries may also be affected in children with low birth weight. The elasticity of the aorta is important to maintain the blood flow and the diastole coronary artery disease. The reduced elasticity of the aorta is a marker of cardiovascular disease [98], and is associated with hypertension and left ventricular hypertrophy due to increased work [99,100]. The men and women of 50 years with low birth weight were reduced complication in the large arteries of the trunk and legs [101]. Martyn and Greenwald [100] suggest that there may be a defect in the synthesis of escleroprotein-elastin in the case of low birth weight. The elasticity of the great arteries depends on the ELASTIN [102] but this elasticity is lost slowly over the years. Optimal function in humans could be approximately 40 years [103]. Once reduced elastin, the arteries become rigid. Which leads to increase in blood pressure. The old age increases the loss of elastin. In the foetus with growth retardation, there are changes in blood flow in various vascular beds, including cerebral vessels and the aorta [104,105].

It is assumed that there is an adaptation of saving body to facilitate the flow in the brain [106]. The electrocardiogram shows that foetuses with growth retardation have hypertrophy of both ventricles [107,108]. Cardiac myocytes are well-differentiated before birth and its rate of maturation is influenced by the load on the heart. Early pressure loads few but large myocytes. Left ventricular enlargement is known as a predictor of morbidity and death from heart disease, independently [109]. Even in the retinal vessels found abnormalities of blood flow in children with low birth weight (branching angles close) [110].

### Nervous system

People with high blood pressure tends to have a higher heart rate [111]. This is associated with a high heart flow, hyperdynamic circulation. Which reveals the activity of the sympathetic nervous system increased [112].

A study in Preston in women and men with low birth weight showed that there is a relationship with a resting pulse rate of the highest [113]. This is consistent with the hypothesis that a sympathetic activity is established in the uterus in the child with retarded growth and leads to an increase in blood pressure in the adult life [60] but the swelling can equally affect both systems. Our observations indicate that there has been an increase in children with these disorders, some are manifest with symptoms parasympathetic, with hypotonia, laziness, sedentary lifestyle, hypersomnia, muscle weakness, etc. Others with increased motor activity with real hiperquenesia. These children are likely therefore to any deviation autonomous or even a familial dysautonomia, common in the adult life of the time.

### Type II diabetes

Insulin plays a central role in the foetal growth and disorders of glucose metabolism and insulin therefore relates to cardiovascular disease and with the early growth [114]. Although it is known that a sedentary lifestyle and obesity are involved in the development of diabetes mellitus type II and family history are important, several studies confirm the association between low birth weight and the altered glucose metabolism and diabetes type II [74,80,115-118]. Among the Pima Indians in the USA, the ratio for diabetes was 3.8 in men and women who weighed less than 2.5 kg at birth [119] but in addition, it has been shown that the pathological loss of weight at birth predisposes to diabetes and glucose intolerance [117] and in the Pima Indians also the association of greater weight to 4.5 kilos in the same way had an increase of type II diabetes [119]. The insulin resistance syndrome is also higher in children with low birth weight [120,121] fact that intensifies if the body mass index is highest in the adult individual.

In San Antonio, Texas, a recent study confirmed the association of low birth weight with insulin resistance syndrome in a population of Mexican American and non-Hispanic whites [122]. In the same way, the low birth weight correlated with an increase in the plasma concentrations of insulin when young adults fasted and then were subjected to a standard glucose challenge [123]. Children between the ages of 10 and 11 years with low birth weight, however, plasma concentrations of insulin in the fasting and after glucose challenge. In any case, the levels of glucose were not altered by this [124]. Forrester et al. [125] found no association between emaciated children at birth and reduced glucose tolerance and in whom serum glycosylated

haemoglobin levels increase progressively when the children had 52 cm. or more at birth and with heights of 46 cm. or less.

The quantification of precursor of insulin in the plasma is high in children with low birth weight, or at one year of age [80] this shows that the individual may have insulin resistance syndrome and sustain the glucose homeostasis from early on in life and not become clinically evident. Full term infants with low birth weight have reduced arm circumference, which implies that they have a low muscle mass as well as less subcutaneous fat [126]. Therefore, according to Barker [60] it is possible that the weight loss at birth is associated with abnormalities in the muscle structure and defects that occur in pregnancy media, can persist throughout life, which may interfere with the ability of insulin to glucose uptake. It has been shown that children with low birth weight (Magnetic resonance spectroscopy studies have low rates of glycolysis and low glycolytic ATP production during exercise [127].

In response to malnutrition, the foetus can reduce their dependence on glucose metabolism and increase the oxidation of other substrates, including amino acids and lactate. This leads to the assumption that the savings of glucose metabolism persists in adult life, which enhances the development of insulin resistance syndrome, with decreased glucose oxidation rates in the peripheral tissues sensitive to insulin. When the availability of nutrients is restricted, the concentrations of anabolic hormones (insulin and IGF-1) decrease, while the catabolic hormones (glucocorticoids) increase. The persistence of these alterations may be the cause of insulin resistance syndrome. [60].

Infants with low birth weight have less beta cells in the pancreas [128]. Although there is no agreement on whether the beta cell mass is reduced in patients with type II diabetes [129]. It appears that nutritional factors and other factors that determine the foetal and infant growth also influence the function and the size of the pancreatic beta cells of the adult. In such a way that the onset of type II diabetes will be determined by the rate of wear or exhaustion of the beta cells with age and for the development of insulin resistance, where obesity is an important factor [130].

In Mysore, South India, men and women with type II diabetes, showed signs of insulin resistance and insulin deficiency [131]. The glucose test showed a slow increase of insulin with the intake of glucose, indicating that there was deficiency, as well as resistance. These findings may suggest the etiopathogeny of the epidemic of type II diabetes in the populations of India located in the urban area: poor nutrition foetal predisposes to the Indian population to resistance to insulin [132]. With the migration to the city, the physical activity decreases and often the income increases which allows higher intake of food [133]. This leads to obesity and insulin resistance. These mothers are unable to maintain the homeostasis of insulin during pregnancy, even with low levels of obesity, become hyperglycaemias, not necessarily with diabetes. This hyperglycaemia affects the size of the child, resulting in foetal macrosomia [134].

Studies show that the neonate of low height and low birth weight, head circumference relative to its size, even within the normal range, persists with disturbances in the metabolism of cholesterol and blood clotting [135,136]. The disproportion of body size with the size of the skull is assumed to be a result of poor nutrition late in gestation [137,138]. This affects the growth of the liver, who regulates the metabolism of cholesterol and blood clotting. These two situations are important organic alterations that have to do with the pathogenesis of cardiovascular disease.

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