

## **Emerging Terms and Concepts of Pharmacotoxicologic Programming/ Imprinting and Embedding, as Related to the Ontopathogeny of Respiratory and Other Disorders**

**Viktor I Goudochnikov\***

*Council of International Society for DOHaD, Santa Maria - RS, Brazil*

**\*Corresponding Author:** Viktor I Goudochnikov, Council of International Society for DOHaD, Santa Maria - RS, Brazil.

**Received:** April 13, 2018; **Published:** May 22, 2018

### **Abbreviations**

DOHaD: Developmental Origins of Health and Disease; GC: Glucocorticoids

The phenomena of programming/imprinting are now well known in the paradigm of Developmental Origins of Health and Disease (DOHaD). Their definition is related to the influence of various factors in critical periods, including perinatal one, with the consequences till adult state and even senescence. For example, intrauterine growth retardation caused by undernutrition can result in lower birth weight, and this alteration in turn may increase the risk of several age-related disorders, including systemic arterial hypertension, diabetes mellitus type 2, osteoporosis, etc [1]. In the mechanisms of programming/imprinting phenomena, endogenous and exogenous glucocorticoids (GC) appear to play essential role [2], justifying our focus on such hormonal drugs in this article.

In 2002 British obstetricians Helen Bayliss and her colleagues [3] were the first to offer a term “pharmacological programming”, in order to describe the consequences of using beta-blockers like atenolol during pregnancy. Somewhat later we proposed to employ a broader term “pharmacotoxicologic programming”, especially stressing adverse impact of drug use in critical periods of ontogeny [4,5]. We suppose that this term may be applied for describing long-term consequences of GC utilization in perinatal period.

Moreover, recently we have offered a term “ontopathogeny” that characterizes the pathogeny of various disorders along the whole scale of ontogeny, both pre- and postnatal [6,7].

What for the term “biological embedding”, it is used preferably to describe cumulative changes in biological systems, for example under the influence of chronic stress during childhood and adolescence [8]. Till the presence moment, nobody used this term to characterize cumulative alterations caused by chronic drug utilization. Here we introduce for the first time a term “pharmacotoxicologic embedding”, in order to describe cumulative changes provoked by chronic treatment with GC and other drugs.

Let’s discuss now the applications of these terms to some respiratory disorders. It is well known that GC, both systemic and inhaled, are widely used for treating bronchial asthma [9,10]. Obviously, in the case of inhalatory mode the systemic changes caused by chronic GC are minimal, at least in low dose range. However, their local influence in airways may be quite substantial. Therefore, we ought to consider pharmacotoxicologic embedding phenomena caused by chronic use of even inhaled GC.

On the other hand, systemic GC use to treat respiratory disorders in neonatal period can provoke pharmacotoxicologic programming/imprinting phenomena that may be important for characterizing the ontopathogeny of various disorders [11].

In conclusion, the new terms offered by us (pharmacotoxicologic programming/imprinting and embedding, ontopathogeny) and by other authors [3] may be quite useful for development of updated concepts related to respiratory and other disorders. The main task at present is to widen the use of new terms in various areas, especially in pharmacoepidemiology and drug surveillance, stressing principally the pharmacotherapy in special groups of patients including children, pregnant women and elderly.

Of course, we understand quite clearly that it is impossible to treat the majority of respiratory and other diseases without GC. In contrast, we suggest only that their use should be optimized, finding the ways to diminish their adverse actions, both short and long-term. One of such ways may be the employment of antioxidants, both well-known (vitamins C and E) and new (like SkQ1) for counteracting the capacity of GC to increase oxidative stress. In this sense, it is very important that antioxidants are able probably to cancel, at least partially, the pharmacotoxicologic programming/imprinting and embedding phenomena caused by GC use in perinatal period and adulthood respectively [12,13].

Another way may be the use of antistress hormones including melatonin and neuroactive steroids, as well as somatolactogens and related peptides (oxytocin and insulin-like growth factor type I) for counteracting adverse actions of GC, again both in perinatal period [14] and in adult state [15,16].

Nevertheless, it should be underlined that all these proposals need to be proved more carefully in further investigations, at first in preclinical studies on experimental models of laboratory animals and thereafter, in clinical trials.

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**Volume 7 Issue 6 June 2018**

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