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# Metamorphosis-like Process in Ontogeny: Possible Mechanisms and Association with Transition from Development to Aging

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## Abstract

Metamorphosis is a well-known biological phenomenon in insects and amphibian species. However, possible existence of metamorphosis-like process only began to be discussed just recently for higher mammals and humans. Therefore we analyzed the literature on periodization of ontogeny, together with our own data based on evaluation of log-transformed plots of body growth and concerning developmental transitions (infantile, juvenile and pubertal) in humans and laboratory animals. Besides, our model of adenohypophyseal cytodifferone was employed, in conjunction with modified scheme of adrenal cortex streaming (including endogenous ouabain) linked to environmental changes in evolution of vertebrates. The analysis performed demonstrates that juvenile transition occurs at the age of 6-8 years in humans that may be considered as critical time period of metamorphosis-like process with appearance of permanent teeth. Earlier the same period was referred to as candidate transition from development to aging. We suppose that juvenile transition is associated with TSH / thyroid and ACTH / adrenocortical axes maturation and on the other hand, with a switch to combined hyperplastic / hypertrophic mechanism of body growth. It seems that transition from development to aging coincides with metamorphosis-like process, being accompanied by inversion of mortality trend from diminution to increase and by activated production of putative hypophyseal inhibitor of metabolism. The connections of these events to phenomenon of aging retardation induced by caloric restriction or hypophysectomy and to age-related increase in metabolic syndrome occurrence are also discussed.

**Keywords:** Metamorphosis; Development; Aging; Ontogeny

## Abbreviations

ACTH: Adrenocorticotropic Hormone; FSH: Follicle-Stimulating Hormone; GH: Growth Hormone; LH: Luteinizing Hormone; PRL: Prolactin; TSH: Thyroid-Stimulating Hormone.

## Introduction

This short communication is an updated version of our work first presented in 2005 at the 18th World Congress of IAGG in Rio de Janeiro, Brazil and published in abstracts [1]. However, such work had much earlier historical bases, beginning from our participation in Leonid A. Gavrilov's seminar on biological faculty of Moscow State University in the decade of seventies of the last century, crossing the decade of eighties with our short publications in the annals of Gerontology Section of Moscow Society of Naturalists (MOIP) and continuing in the decade of nineties by our communications on various events organized by Brazilian Society of Gerontology and Geriatrics (SBGG), including national and local events in Rio de Janeiro and São Paulo.

Besides, we never tried to study only aging period separately, but instead, we explored ontogeny as a whole, being interested especially in transition from development to aging. Therefore, it was logical for us to participate since 2009 in the activities of International Society for DOHaD (Development Origins of Health and Disease), becoming finally in 2011 a member of its Council. Therefore, an update performed in present communication is related principally to the role of glucocorticoids and other hormones in the mechanisms of programming/imprinting and embedding phenomena.

## Main Part

### Metamorphosis in Insects and Amphibian Species

Metamorphosis is as well-known biological phenomenon in insects. An accepted paradigm affirms that it is a process regulated by hormones, with principal contribution of ecdysteroids and juvenile hormone [2]. On the other hand, metamorphosis is a well-known phenomenon also in amphibian species, with the main regulatory influence of thyroid and glucocorticoid hormones [3,4].

However, the possible existence of metamorphosis-like phenomenon in higher mammals only began to be discussed just recently: in 2014 Buchholz [5] and in 2017 Zgurskiy [6] suggested a metamorphosis-like process in perinatal and pubertal period respectively. In this sense, we believe that comparative biological approach can help to advance in theoretical studies on complex interrelationship between the stages of ontogeny.

### Periodization of Ontogeny

Earlier we have used log-transformed plots of body growth in rats and humans, in order to reveal possible transitions between developmental stages [7]. These studies have shown the existence of three transitions: infantile, juvenile and pubertal. Infantile transition was observed only in humans; however the other two transitions were obvious in both species. In rats these two transitions occurred at the age of three and five weeks approximately. In humans they occurred at the age of 6–8 and 12–14 years respectively.

It is interesting that such transitions may be based on switches between different mechanisms of growth: from predominantly hyperplastic growth to the combination of hyperplastic and hypertrophic growth during juvenile transition and from the last to predominantly hypertrophic growth during pubertal transition [8].

### Model of Adenohypophyseal Cytodifferone

Previously we have offered a model of adenohypophyseal differone [9], according to which there exists the following sequence:

Stem or progenitor cell → corticotroph (ACTH) → thyrotroph (TSH) → gonadotroph (LH/FSH) somatomammotroph (GH PRL)

It is important to consider that this sequence does not mean the transformation of one differentiated cell to another but the sequential commitment of immature precursors, with subsequent differentiation of these precursors to fully differentiated secretary cells.

### Modified Scheme of Adrenal Cortex Streaming

Earlier ouabain was identified as a hormone produced by adrenocortical cells [10]. Besides, some data show tissue streaming in the adrenal cortex [11]. We suggested that ouabain-producing cells may be the stage in adrenocortical cytodifferone that can be expressed as:

Stem or progenitor cell aldosterone → cortisol (corticosterone) → ouabain → adrenocortical androgens

The same consideration as for adenohypophyseal differone is important for this sequence also (see section 3).

There may be such correlations between two cytodifferones (adenohypophyseal and adrenocortical):

ACTH → aldosterone / cortisol (corticosterone)

TSH → ouabain

LH/FSH → adrenocortical androgens

### Environmental Changes in Evolution of Vertebrates

It seems that two cytodifferones described above recapitulate the following changes in environment:

a) ACTH and aldosterone / cortisol (corticosterone) may correspond to the change from salt-containing water of oceans and seas to saltless water of rivers and lakes by evolutionary precursors of some fishes;

b) TSH and ouabain may be related to changes from saltless water to the shore land by amphibian species;

c) LH/FSH and GH/PRL, as well as adrenocortical androgens may correspond to change from shore land to distant land in reptiles and mammals and to change from land to air in birds.

### Juvenile Transition

All the suggestions made above, as well as theoretical analysis performed earlier allow us to affirm the following: critical point of mammalian (and human) ontogeny corresponds to juvenile transition regulated probably by thyroid and adrenocortical axes maturation. Among vertebrates, in fish this transition is not revealed yet, whereas in reptiles, mammals and birds it becomes hidden, being obvious only in amphibian species. However, some traces of this process remained, and we believe that mid-growth spurt and change to permanent teeth are two such traces.

From our point of view, it is highly pertinent that inversion of mortality trend from decrease to augment occurs in humans at the age of 8–10 years [12], close to juvenile transition that may be considered, therefore, as landmark of cardinal change from development to aging.

### Comparisons of Three Models of Metamorphosis-like Phenomena

Let's compare three models: ours described earlier [1] and updated here, with that of Buchholz [5] and Zgurskiy [6]. The first and most important difference is the principal transition employed: juvenile in our model, perinatal in the work of Buchholz and pubertal in the model of Zgurskiy. As Buchholz [5] admitted, according to the literature, increases in the levels of glucocorticoid and thyroid hormones occur not only in perinatal period, but also during weaning, at least in rodents, i.e. at the age of approximately three weeks in rats, therefore this stage coincides with juvenile transition revealed by log-transformed plots of somatic growth (see section 2).

In addition, the maximal growth rate corresponding to inflection of growth curve occurs, at least in sheep, earlier than pubertal transition revealed by augment of progesterone level [13]. Finally, the timing of puberty in humans has changed significantly during the last 100 years, suggesting the influences of perinatal and early postnatal environmental factors [14]. Resuming these considerations, our model of metamorphosis-like process, based on juvenile transition, has its own advantages, as compared to models of Buchholz and Zgurskiy. Nevertheless, it should be underlined that the problem of ontogenetic periodization is not settled yet sufficiently and therefore, it is open for further experimental research and theoretical modeling.

### Hypophyseal Inhibitor

Since 1974, when Denckla [15] suggested the presence of metabolic inhibitor in pituitary gland, there were, unfortunately, only few experimental studies on this interesting aspect of endocrine regulation. However, from theoretical point of view, earlier we supposed that indeed, anterior pituitary gland might produce unidentified protein that could be isolated by preparative PAGE in mildly acidic conditions [16].

Till the present moment, the only two procedures were confirmed to postpone aging and/or enhance mammalian life span: caloric restriction and hypophysectomy [17]. It is important that sometimes, caloric restriction is considered as "physiologic hypophysectomy". Previously we suggested that anti-aging influence of both experimental procedures might be related to removal of putative hypophyseal inhibitor [18].

At last, we suggested that age-related increase in metabolic syndrome occurrence may be explained by accumulation of putative metabolic inhibitor in pituitary gland [19]. This allows to explain, why there occurs a decrease in physical activity with aging and especially, as referred to relative protection from the influence of radical oxygen species on macromolecules, principally mitochondrial ones.

### Links to DOHaD Paradigm

At present, glucocorticoids are considered as principal mediators of perinatal and early postnatal phenomena of programming/imprinting and embedding. However, our recent analyses clearly demonstrate that glucocorticoids interact with other hormones, including thyroid hormones [16], as well as melatonin, neuroactive steroids, GH/PRL and related peptides, interleukins [20–23] both during development and in adult state. Therefore, it is important to consider hormonal interactions in future theoretical investigations of developmental transitions, as well as the main ontogenetic transition from development to aging.

## Conclusion

We are aware that our proposals may be considered, at least in part, as preliminary theoretical constructions only. Indeed, a lot of experimental data should be obtained yet, in order to clarify, confirm or reject these proposals. Nevertheless, we think that our theoretical study may be a starting point for establishing new hypotheses that can be tested in experimental work. Therefore, we shall be glad to receive suggestions of joint research interventions, since it is our conviction that in globalized world only network-based teams may function efficiently, not depending on places where their participants are located.

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