



Environment- and gene-dependent human ontogenesis, sociogenesis and phylogenesis (eco-geno-onto-socio-phylogenesis)

Günter Dörner

Institute of Experimental Endocrinology, Humboldt University Medical School (Charité),
Berlin, GERMANY.

Correspondence to: Prof. Dr. med. Dr. h.c. Günter Dörner, Director emeritus,
Institute of Experimental Endocrinology,
Humboldt University Medical School (Charité),
10117 Berlin, Schumannstr. 20/21, GERMANY
EMAIL: expendo@charite.de

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Abstract

Prevention of environment- and gene-dependent, teratogenic malfunctions (“Functional Teratogenesis”) – caused by abnormal hormone, neurotransmitter and cytokine concentrations during organization of the neuro-endocrine-immune system (NEIS) should be considered as a global challenge of outstanding relevance. By optimizing the natural and social environment and correcting in time abnormal concentrations of hormones, neurotransmitters and cytokines during the critical perinatal (pre- and early postnatal) organization period of the NEIS (“Neuro-Endocrine-Immune Prophylaxis”) human ontogenesis and sociogenesis can be decisively improved (“Primary Prevention of Maldevelopments of Human Beings and their Societies”). Finally, phylogenesis is dependent on incessant sequencies of ontogenesis and sociogenesis (“Onto-Socio-Phylogenesis”).

Introduction

For about 4 decades we have performed extensive experimental, clinical and epidemiological studies of epigenetic effects of the perinatal (pre- and early postnatal) natural and social environment on the ontogenesis, mediated by chemical messengers, i.e. by hormones neurotransmitters and cytokines. In this context, we have recognized and reported that hormones, neurotransmitters and cytokines are not only temporary stimuli or inhibitors of physiological and psychological processes throughout life. But in critical perinatal developmental periods of the neuro-endocrine-immune system (NEIS), they represent developmental signals i.e. organizers or “ontogenes”, which preprogramme the expressivity of specific genes of the NEIS for the entire life [4–18].

The NEIS, which controls fundamental processes of life – such as reproduction, metabolism, growth information processing and immune responsiveness – consists of the nervous system (NS), the endocrine system (ES) and the immune system (IS). The brain is the central controller of the entire NEIS. It operates by neurotransmitters and neurohormones on the ES and IS. The ES operates by hormones on the NS and IS, and the IS by cytokines and antibodies on the NS and ES. Therefore, alterations of the NS, ES and IS can also result in alterations of the other both systems.

Functional Teratology

During critical developmental periods of the NEIS, neurotransmitters, hormones and cytokines, when occurring in unphysiological concentrations – can be effective as endogenous malorganizers, i.e. as “endogenous teratogens” and result in life-long functional disturbances and important diseases. Thus, I have founded “Functional Teratology” 28 years ago, i.e. structural teratology or teratomorphology as the science of malformations was supplemented by “functional teratology” or teratophysiology and teratopsychology as the science of perinatally acquired life-long malfunctions [4, 5].

In my opinion, important endemic diseases can be based essentially on perinatal environmental processes, caused by unphysiological concentrations of neurotransmitters, hormones and cytokines. In this context, I would like to mention some examples of our extensive experimental, clinical and epidemiological findings [4–18, 23]:

- (1) After massive application of environmental chemicals with estrogenic, antiandrogenic and antigestagenic effects as well as neurotransmitter (acetylcholine) blocking effects in East-Germany since the 1950-ies – especially of the pesticide DDT as paradigm – we could observe a significant increase of polycystic ovaries, sub- or infertility and breast cancer in women, of disturbances of spermatogenesis, sub- or infertility and testicular cancer in men as well as of immature and dead births and backward children. Even significant correlations between the concentrations of DDT and its metabolites in body fluids at the time of birth and the incidence of such disturbances were found.
- (2) In contrast, after prohibition of DDT application in West-Germany at the early 1970-ies, but in East-Germany only at the end of the 1980-ies, we could observe in those born after this period – parallel to the decrease of the concentration of DDT and its metabolites – a significant decrease of such teratogenic functional disturbances. However, reduction of deficient spermatogenesis – as well as of testicular cancer – could only be observed in West-Germany during the last years. In this context, we must take into consideration that those born in East-Germany after prohibition of DDT-application have not yet reached sexual maturity.
- (3) Early postnatal overnutrition in animals and human beings gave rise to a significant increase of obesity in later life [13]. Obesity is again a decisive cause for the aetiology of the metabolic syndrome, diabetes mellitus and arteriosclerosis, which predispose again to heart infarction and apoplexy. Our findings obtained in the 1970-ies in 500 children [13] were recently clearly confirmed by Stettler et al [27] in more than 20.000 children.
- (4) Perinatal quantitative and qualitative malnutrition, i.e. undernutrition and overnutrition as well as deficient breast-feeding, associated with the demonstration of unphysiological concentrations of neurotransmitters or their precursors – when occurring during brain differentiation – resulted in a life-long decrease of learning and memory capacities.
- (5) Early postnatal maternal deprivation also gave rise to a persistent significant decrease of learning capability in animals and human beings. In this case a significant postnatal decrease of acetylcholine was demonstrated in the brain of animals. By simultaneous early postnatal administration of the acetylcholine esterase inhibitor pyridostigmine the acetylcholine decrease and the persistent disturbance of learning capacity could be prohibited [19]. In maternally deprived babies of day-nurseries we found significantly decreased mental and psychosocial capacities at school age. Hence, we were able to introduce a so-called “baby-year“ in East-Germany since the 1970-ies, associated with temporary unemployment and complete payment of the mother’s salary for one year after birth.
- (6) In the offspring of pregnant mother rats with artificial diabetes mellitus, a diabetic metabolism was produced over several generations. Subsequently, the prevalence of childhood-onset diabetes could be reduced to 1/3 in East-Berlin during the 1980-ies by optimizing the diagnosis and therapy of gestational diabetes. Recently, we could demonstrate that the prevalence of childhood-onset diabetes was only half as high in East-Germany as compared to West-Germany shortly before the reunification of Germany. Following the break-down of a specific care system for diabetes mellitus in East-Germany after the reunification, we could observe a 3.5-fold increase of the childhood-onset diabetes. Consequently, the childhood-onset diabetes was found to be now even more frequent in East – than in West-Germany [15].
- (7) In adult rats, following perinatal administration of the cytokine interleukin-1 β – which is overproduced during viral infections – we could observe a dysplasia of the region entorhinalis in the limbic brain. Similar brain alterations were found by Beckmann and Jacob [3] in schizophrenics, whose mothers had endured an epidemic influenza during gestation.
- (8) Experimental findings of our own and clinical data of other authors suggest that the strong increase of allergic diseases observed during the post decades may be also based – at least in part – on environment-dependent perinatal developmental disturbances of functional teratogenesis of the NEIS [11]. In 1998, the term “toxicant-induced loss of tolerance” (TILT) was inaugurated by Ashford and Miller for the explanation of a strong hypersensitivity against environmental chemicals, which was worldwide noticed [2]. In my opinion this term corresponds to the term “teratogen-induced alteration of tolerance” used by our group since the 1970-ies. Thus, the tolerance of the NEIS against environmental burden can be irreversibly diminished by “functional teratogens” e.g. by unphysiological

concentrations of hormones, neurotransmitter and cytokines [10].

- (9) We could demonstrate by experimental, clinical and epidemiological data that genuine bi- and homosexuality as natural variants of sexual orientation can be based – as well as transsexuality – on a gene- or environment-dependent variability of prenatal sex hormone concentrations. Hence, we demanded successfully a dediscrimination, decriminalization and depathologization of bi- and homosexuality and a complete tolerance and acceptance as well as the same right for bi- and homosexuals as for heterosexuals [14].
- (10) Most recently, we succeeded in demonstrating – even after statistical adjustment to the socioeconomic status – a significant inverse correlation between the mental capacities of pupils at 15 years of age, which we obtained by the PISA study in countries of 4 continents, and the DDT-contents in mother milk during the years of their birth [16]. Similar findings were observed for the 16 Federal States of Germany [16]. In animal experiments, Eriksson et al. [19] observed after early postnatal DDT-administration a significantly decreased learning capacity throughout life, associated with reduced activities of muscarinergic acetylcholine receptors in the brain.

Neuro-Endocrine-Immune Prophylaxis

The foundation of “functional teratology” in the 1970-ies was supplemented by a “neuro-endocrine prophylaxis” and “neuro-endocrine-immune prophylaxis” in the 1980-ies with the following demands for pre- and early postnatal organization periods of the NEIS.

- (1) Optimizing iodine prophylaxis;
- (2) Improvement of diagnosis and treatment of gestational diabetes mellitus;
- (3) Prohibition of oxygen deficiencies in fetuses and newborns;
- (4) Prohibition of stressful situations in pregnant women, newborns and babies;
- (5) Optimizing the treatment of gestoses; preventing infections – especially by optimizing immune prophylaxis – and prevention of hypovitaminoses;
- (6) Avoidance of pre- and early postnatal under- and overnutrition as well as qualitative malnutrition; strengthening of breast-feeding;
- (7) Prohibition of radiation in pregnant women, embryos and fetuses and young children; most of all, worldwide prohibition of environmental chemicals with “functional-teratogenic effects” and systematically testing of such substances in animal experiments before their application for human beings;
- (8) Strict avoidance of alcohol, nicotine, drugs and potentially functional-teratogenic medicaments during pregnancy and breast-feeding;
- (9) Prohibition of psychosocial deprivation in newborns, babies and children;
- (10) Improvement of the neuroendocrinological and genetic diagnosis of inborn disturbances of me-

tabolism and correction in time of unphysiological concentrations of hormones, neurotransmitters and cytokines caused by genetic defects, e.g. inborn adrenocortical hyperplasia, hypothyroidism or phenylketonuria.

In my opinion, with the aid of such preventive measures – particularly by optimizing pre- and early postnatal nutrition and vaccination, by prohibition of environmental chemicals as “neuro-endocrine teratogens”, by prevention of prenatal stressful situations, alcohol, nicotine and drugs as well as of early postnatal social deprivation and by correction in time of genetically conditioned unphysiological concentrations of hormones, neurotransmitters and cytokines – life-long malfunctions of the NEIS and dispositions for important diseases can be prevented in millions of human beings, and their life-long physical, psychical or mental capacities may be essentially improved.

Onto-Sociogenesis

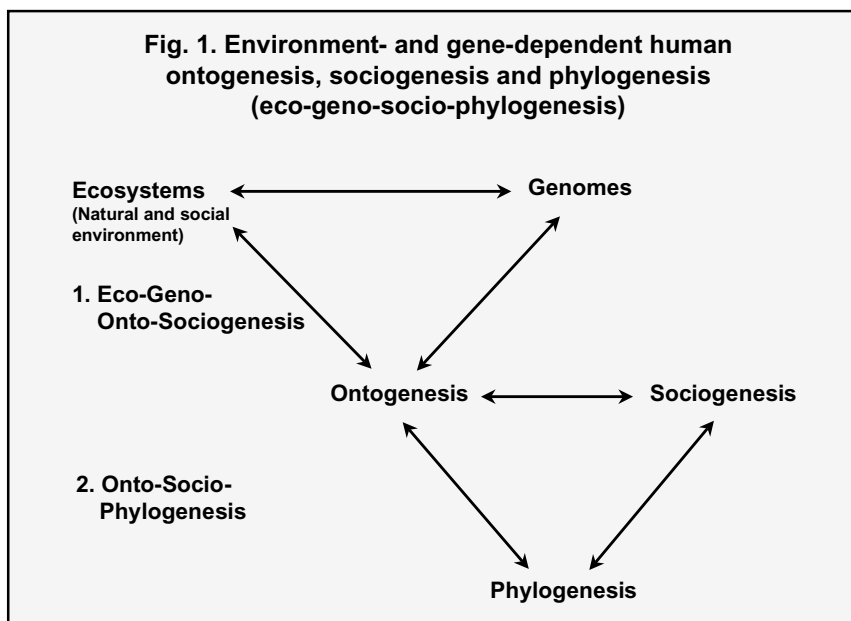
Recently, I could obtain from the German Office for Statistics in Wiesbaden and other institutions nationwide epidemiological data which suggest that pre- and early postnatally acquired teratogenic defects of the NEIS – caused by the natural and psychosocial environment – cannot only exert lasting negative effects on health and education, but also on other social and economic systems, e.g. for family and children, security and legality as well as for labour market, finances and economy.

All the systems are also influenced by fertility-dependent demography. Thus, we have found a significant inverse correlation between the DDT-content in the mother milk and the fertility of the offspring. The higher the DDT-content in the mother milk during the 1970-ies, the lower was the ratio of live births/deaths during the 1990-ies. The ratios of live birth/deaths displayed an inverse correlation with the demographic process of overaging, affecting again the costs for health and pension systems and the budget deficits of the 16 Federal States of Germany.

We have also found a significant correlation between the DDT-content in the mother milk during the 1970-ies and partial maternal deprivation 1998, e.g. percentages of babies and young children with < 3 years of age in day-nurseries, as well as prevalences of illegitimate children and divorces.

As early as in the 1970-ies, Fox et al. [18] observed strong disturbances of breeding care in birds after application of organic chlor compounds, such as DDT and its metabolites. In addition, Anderson et al. [1] had already published that androgens in pregnant rabbits resulted in a disturbed care of the young animals by the mothers and even by the mothers of their offspring. In this context it should be mentioned that we could demonstrate, indeed, a clear-cut increase of adrenal androgens after administration of DDT in rats.

Additional positive correlations were found between the DDT-content in the mother milk and early



postnatal maternal deprivation with the frequencies of children and juveniles under suspicion of criminal acts in Germany and with corruption index of adults in different countries, as registered by “Transparency International”.

All the findings suggest a significant interrelationship between the perinatal environment- and gene-dependent ontogenesis of human beings and the quality of their societies (sociogenesis). Therefore, I would like to name these interrelated developing processes of human beings and their social systems as “Human Eco-Geno-Onto-Sociogenesis” (Fig.1).

The Federal States of Germany Bavaria and Baden-Württemberg, which displayed the lowest values of DDT in mother milk and of maternal deprivation in early postnatal life, respectively, also showed the most favourable individual and social outcomes, i.e. the highest values for health (lowest sick notes) and life expectancy, fertility (live birth/deaths), education (PISA-studies), security (lowest criminality), labour market /lowest unemployment rates) and economy (lowest budgetary deficits) of all 16 Federal States in Germany.

These observations support the thesis that by optimizing the pre- and early postnatal natural and psychosocial environment during the organization of the NEIS, many crisis-prone individual and social developmental processes are avoidable. Such primary preventive measures for the eco-geno-onto-sociogenesis appear even improvable under selective consideration of specific mutations and polymorphisms. The organization period of the NEIS consists of the critical pre- and early postnatal differentiation period followed by a maturation period, reaching up to early adulthood. It should be mentioned that functional teratogenic defects of the NEIS produced during the critical perinatal differentiation period can be partly compensated by enrichment of the environment and correction of

unphysiological neurotransmitter concentrations in the brain during the maturation period [21, 23].

In my opinion, the relevance of optimizing the natural and social environment for the differentiation of billions of omni- or at least multipotential stem cells during the organization of the NEIS appears to be much greater than the preparation of pre- or also postnatal stem cells for specific implantations in defective organs or tissues.

After we had supplemented “Structural Teratology” by “Functional Teratology” in the 1970-ies, geneticists have supplemented “Structural Genomics” by “Functional Genomics” in the late 1990-ies [21, 25]. In my opinion “Functional Teratology” represents a decisive part of “Functional Genomics” for primary preventive measure for individuals and social systems as well, since “Functional Teratogenesis” as well as “Eco-Geno-Onto-Sociogenesis” are based essentially on environment-dependent, life-long enduring alterations of gene expressions, which are pre-programmed by neurotransmitters, hormones and cytokines in pre- and early postnatal life.

In 2001, the First World Congress on “Fetal Origin of Adult Diseases” was organized by Barker and associates in India, where our Institute took part with 6 scientific contributions. In 2003, the Second World Congress on this topic was already carried out in England. At this meeting an “International Society for Developmental Origins of Health and Adult Diseases” was founded. In this context, it should be mentioned that an interdisciplinary cooperation and association for “Human Ontogenesis” was founded in the late 1980-ies and early 1990-ies by our group in Berlin (K.F. Wessel, G. Dörner and G. Tembrock) followed by a “Society for Human Ontogenesis” (“Humanontogenetik”) in 2000, while P.G. Fedor-Freybergh has founded – supported by our group – an “International Society for Pre- and Perinatal Psychology and Medicine” as early as 1989.

Now I hope that the knowledge of "Functional Teratogenesis", "Neuro-Endocrine-Immune Prophylaxis" and "Eco-Geno-Onto-Sociogenesis" supported by national and international societies and a "US-task force" for cooperation of geneticists and environmental scientists [24], may successfully promote a worldwide positive development of millions or even billions of human individuals and their social systems as well.

Onto-Socio-Phylogenesis

The phylogenesis is the result of incessant sequences of ontogenesis and sociogenesis, based on interrelationships between ecosystems (natural and social environment) and genomes (Fig. 1).

In my opinion, human-made changes of the natural and social environment appear to be nowadays the most important factors for ontogenesis, for sociogenesis and even for phylogenesis.

Editor's and publisher's note:

We from the Neuroendocrinology Letters most cordially congratulate Professor Dörner on his 75th birthday on July 13, 2004. A Symposium honoring the life and work of Professor Dörner will take place on July 16, 2004 in the Charité, Humboldt University, Berlin. Professor Dörner has been for the past 30 years a very close and faithful friend, both of the late Derek Gupta, the founder and former Editor-in-Chief of the Neuroendocrinology Letters, as well as my dear personal friend, giving me his consistent, most valuable support and advise. We wish Professor Günter Dörner many more fruitful years in continuing his invaluable work in full and good health and high life quality, together with his wonderful wife, Hildegard, standing by and supporting him at all times, sunny and cloudy days, with her unconditional love. Ad multus Annos!

*Most cordially and respectfully,
on behalf of the Neuroendocrinology Letters,
Peter G. Fedor-Freybergh, Editor-in-Chief*

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