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Forum

Imprinting of paths of heterodifferentiation by prenatal or neonatal exposure to hormones, pharmaceuticals, pollutants and other agents or conditions

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Introduction

Since the first reports associating the development of clear cell cervicovaginal adenocarcinomas in young women with a treatment of their mothers with diethylstilbestrol during pregnancy [1-3], con-firmed in studies with experimental animals [4, 5], it was clear that prenatal exposure to this synthetic estrogen induces permanent changes in some cell types. These changes become evident as late as after puberty onset as an enhanced risk for malignant cell transfor-mation, probably under the effect of postpubertal increased estrogen levels in the blood.

Based on the above information, György Csaba and his co-workers started an experimental study that allowed the demonstration that exposure of fetuses to some hormonally active agents during critical periods of their development induces permanent changes in the action of related hormones [6, 7]. These changes can be detected later in adulthood as a modification in the activity of receptors and in the intensity of responses mediated by them [8, 9].

Csaba [7, 9] has given the name "imprinting" to this effect of hormones during fetal or neonatal life in permanently modifying the ability of the cells to react to hormone stimulation during adulthood.

Causes of "imprinting"

Recent findings demonstrate however that the process called "imprinting" may be induced, in addition to hormones, by various pharmaceuticals, polluting agents, food components ingested by the mother, maternal stress, and several other agents or conditions that interact with the different cell-types at precise stages of their fetal or neonatal development (*vide infra*). Further, this process does not only involve a change in quantity and quality of hormone receptors in affected cells once they reach maturity, but it also involves several biochemical, morphological and functional changes. Therefore, taking into consideration that the process discovered by Csaba really involves a modification of the routes of normal differentiation of these cells, we propose to rename it as "imprinting of paths of heterodifferentiation". The changes in cell differentiation induced by this mechanism may lead, later in adulthood, to the development of various diseases, such as neoplasias, endocrine abnormalities, infertility, immune diseases, psychologic alterations, or changes in personality and behavior. The enormous importance of this process in the determination of health conditions later on in life takes place in the fact that it is not only generated by agents that it is easy to avoid. It is also induced by early exposure to a myriad of agents and conditions that it is very difficult to detect and avoid, among them stress, very low concentrations of pollutants and natural substances contained in food.

Long-term effects on organs and systems

Many of the xenobiotics that will be described below induce, at relatively high doses, permanent changes in 100% of prenatally exposed experimental animals. At much lower concentrations, these agents may affect a small percentage of exposed human population; therefore the etiology of the diseases induced by them may remain for a long time undetected. These xenobiotics can be absorbed from drinking water (arsenic or other pollutants), air (lead, carbon monoxide, nicotine) or from food (synthetic hormones used as farm animal growth promoters, pesticides, food additives, cadmium, lead, bacteria toxins or mycotoxins, etc.). They may affect an important part of the exposed population determining, as in the case of lead from leaded gasoline, behavioral alterations that in turn may generate deep sociological changes in the next years. Perhaps it will be found in the future that many diseases are determined, at least in part, by prenatal or early postnatal exposures, possibly the fall of ancient civilizations will be explained by the same mechanism, and many dramatic changes for current civilizations or even for Mankind in the future could be foreseen if care will not be taken to avoid exposure to these dangerous compounds.

Research in this new field of the medicine of the future should not be only concerned with the gross effects of exposure to the above agents on the morphology and functions of the different organs and systems; it should be also committed to every of its components. This is specially important if we take into consideration the newly developed concept that several hormones interact with target organs through multiple and independent mechanisms of hormone action, with different kind of receptors for the same hormone (see [10-16] for a review).

This concept arouse from the findings in our Laboratory of different types of estrogen receptors [14, 17, 18], involved in separate groups of responses through independent mechanisms [10, 11, 14, 15, 19], and the dissociation of the different estrogenic responses under various experimental conditions [14, 15, 20-24]. Further studies suggested that glucocorticoids [16, 25, 26] and perhaps many other hormones [12, 15], also act through multiple mechanisms. According to this new concept, harmful agents may modify selected parameters of hormone action but not others. This interaction may not be detected in studies evaluating one mechanism or one parameter of hormone action only [14, 15, 27-30].

Examples are provided below to point to possible health implications in offspring caused by exposure of pregnant mothers to various agents to which people are frequently massively exposed. Only the full understanding of the process of imprinting of paths of heterodifferentiation and a complete knowledge of agents determining these changes may improve the public health conditions in the future and perhaps prevent many diseases of still unknown aetiology.

Effect of perinatal exposure to diethylstilbestrol and other estrogens on the female genital tract

The first informations of the effect of prenatal exposure to diethylstilbestrol in humans were based on the observation of a new type of gynecologic malignancy that develops after puberty or during adult age in daughters of mothers treated with this synthetic estrogen during pregnancy [1-3]. This finding was also confirmed in experimental animals [4, 5].

In addition to increased tumorigenicity, other alterations were described in the genital tract of female offspring after maternal exposure to diethylstilbestrol and other estrogens during pregnancy. In experimental animals, perinatal exposure to diethylstilbestrol, allylestrenol, estradiol-17ß or estradiol benzoate induce permanent changes in steroid hormone activity [9, 31-34], histological alterations in the female genital tract [34, 35], including gross abnormalities [35], development of paraovarian cysts [36] and infertility [37]. In the human species, women prenatally exposed to diethylstilbestrol present histological alterations in the genital tract [2], including gross abnormalities [38, 39], development of paraovarian cysts [36], endometriosis [40], an increased frequency of abortions [3] and infertility [38-40].

The changes in steroid receptors, explaining the modifications of the responses to hormone stimulation and most of the above changes, probably reflect the imprinting of routes of heterodifferentiation of genital tissues following perinatal exposure to diethylstilbestrol or other estrogens. In the mouse, the precocious appearance of estrogen receptors in uterovaginal epithelium [34] may explain the postpubertal increase in adenocarcinomas derived from this tissue. In the human, the abnormal localization of uterine epithelium in the cervix and vagina was considered as one of the factors increasing risk of tumorigenicity [41].

Further, the decrease in estrogen receptors in the rodent uterus following neonatal treatment with diethylstilbestrol, allylestrenol, estradiol-17ß or estradiol benzoate [9, 31-33, 42, 43] may explain the persistent underdevelopment of rat uterine glands [42] and suggest an explanation for uterine hypoplasia in humans [42], in addition to a decrease in the ability of the uterus to respond to estrogen stimulation [31-33, 43].

Effect of perinatal exposure to androgens on the female genital tract

The perinatal exposure of experimental animals to high levels of androgens causes changes in the normal development of fetal genitalia [44, 45], failure in ovulation and corpus luteum formation [44, 46, 47], polycystic ovary development [44, 47, 48], presence of a constantly cornified vaginal epithelium [47, 49], changes in uterine physiology (including abnormal hormone-induced uterine growth [31, 44-46, 49, 50]), a permanent alteration in the hypothalamic cyclic center [51], and sterility [44, 52, 53].

The literature contains conflicting reports on some of these changes. While some investigators did not detect changes in estrogen receptor levels [31, 32, 43] or in estrogen action [31] in the uterus of neonatally androgenized rats, others reported a decrease in receptor levels [50] and an impairment in hormone action [32, 43, 45, 46, 50]. Biochemical techniques not discriminating between changes in the different uterine cell-types were used in these studies.

Considering the possibility of dissociation of responses to estrogen under different experimental conditions [14, 15, 20-24] (*vide supra*), studies were performed in our Laboratories on estrogen action in the uterus of prenatally androgenized rats, using morphometrical techniques that discriminate between responses in the different uterine cell-types. We found that prenatal androgenization inhibits estrogen induced luminal and glandular epithelium hypertrophy, and potentiates endometrial edema, eosinophil migration to the uterus [29] and the mitotic response [30], but does not modify myometrial hypertrophy in the prepubertal rat uterus [29]. This dissociation of responses to estrogen can be explained by the independence between the different mechanisms of estrogen in the uterus [10-16, 19] and the independent regulation of hormone action in every cell-type [14, 54].

What mechanisms bear upon alterations in the physiology of the uterus?

The mechanisms involved in the changes in uterine physiology are not well understood. Perinatal androgenization may be involved in the alteration of the normal development of estrogen receptors [8, 9] in some cell-types only [29, 30]. Other steps of the mechanisms of hormone action may be also affected [43, 46]. Perinatal androgens may modify estrogen action directly [8, 9], or indirectly, through changes in blood levels of other hormones involved in estrogen action regulation. This last possibility is based on changes in blood levels of prolactin [55, 56], estrogens [57], progesterone [58], and a potentiation of the stress-induced events, including the hyperprolactinemic response to stress [59], in neonatally androgenized animals. Indeed, progesterone [54, 60], prolactin [28, 61], and the stress-induced hormones epinephrine [62] and glucocorticoids [63] selectively modify some but not all responses to estrogen.

The selective inhibition of estrogen action in luminal and glandular epithelium cells in androgenized rats is the most conspicuous histological change observed in the uterus. It may contribute to the decrease in fertility observed in these animals [51]. If this effect is confirmed in humans, it may explain changes in fertility in daughters of patients treated with androgens or other steroids during pregnancy and alert population to the possible risk of the ingestion of meet from animals grown with synthetic androgens.

Neurobehavioral effects of perinatal exposure to synthetic androgens, estrogens or progestins

The development of adult sex behavior and other sex-dependent personality characteristics is dependent on the presence of sex hormones during precise stages of intrauterine development in same regions of the brain. These hormones determine paths of neuronal differentiation that are normal for each gender.

In humans, prenatal exposure to low levels of sex steroids per-manently affects personality [64]. Exposure to synthetic estrogens determine in the adult an outer-directed personality, more group-oriented and group-dependent, less individualistic and more iden-tified with its group or social environment. Exposure to synthetic progestins fix in the adult an inner or self-directed personality, more independent, self-assured and self-sufficient, more individualistic and less concerned with its social environment [64].

Perinatal exposure to higher levels of sex steroids or non-steroidal synthetic agonists like diethylstilbestrol determines all life-lasting alterations of sex-dimorphic behavior (gender role), temperamental sex differences and sexual orientations in humans [65-69]. Changes also include alterations in personality dimensions, self-esteem, attitudes toward work and family, mental abilities [67], sex-dimorphic play behavior in children [68] and a decrease in orientation toward parenting in adult women [69].

In countries where meat contamination with hormones is evident [30, 70-73], increased frequency of premature ovary enlargement, ovarian cysts [71], increased estrogen levels in the blood [71, 74], premature telarche and other signs of estrogen activity [71, 74] were found in an important percentage of girls under 3 years of age. A similar increase in sex hormone production may occur in males prenatally or postnatally exposed to synthetic sex hormones, causing behavior abnormalities in adulthood. In extremely violent criminals with an history of violent assassinations or rapes, presence of abnormally high androgen levels in the blood was reported [66]. Perinatal exposure to sex hormones may contribute to the increase of sex hormones levels in some of them, causing changes in their personality.

Other effects of prenatal or early postnatal exposure to synthetic estrogens or androgens

Neonatal androgenization also abolishes clock-timed gonadotrophin release in prepubertal and adult female rodents [75], induces changes in tuberoinfundibular dopamine nerve activity [76] and several biochemical alterations in the forebrain [77], hypothalamus [78-80] and cerebellum [81], including alterations in opioid control of noradrenaline release in specific brain areas [82] and changes in gonadotropin [51], oxytocin [83] and prolactin [55, 56] secretion. Prenatal exposure to estrogens affects subsequent transport of Ó-aminobutyric acid into rat brain [84]. This reflects important changes in the differentiation and development of the central nervous system under the effect of perinatal exposure to synthetic androgens and estrogens, and suggest an explanation for the behavioral changes in exposed experimental animals or humans (*vide supra*).

Androgenization induce permanent alterations in testosterone metabolism in the hypothalamus-pituitary-gonadal axis in male rats [85]. Neonatal exposure to estrogens determine developmental, structural and functional alterations in the testis, prostate and seminal vesicles [86-89].

The immune system is also affected by exposure to sex hormones. Estrogens cause changes in the development of the rat thymus gland, including premature involution of its cortex [90]. Diethylstilbes-trol persistently alters NK cell activity in the mouse [91] and humans [92]. Alterations in immune responsiveness [93] and in-creased occurrence of autoimmune disease [94], in addition to the increased frequency of diseases suggesting impaired immune function, such as respiratory tract infections, asthma, arthritis, and lupus [95], were reported in women exposed *in utero* to diethylstilbestrol.

Imprinting of paths of heterodifferentiation by polypeptide or aminergic hormones

In the rat, neonatal treatments with thyroxine (that decreases TSH levels) [96] or high doses of TSH [6] depress subsequent responsiveness to TSH. Neonatal treatments with vasopressin [97] or met-enkephalin [98], permanently increase sensitivities to vasopressin or opioids. Neonatal exposure to insulin determine in adult rats altered binding of insulin and altered response to the hormone in the liver [99].

Imprinting of paths of heterodifferentiation was found in the chicken ovary for FSH [100].

A neonatal treatment with catecholamines (epinephrine, isoproterenol, dopamine) alters, in the adult rat, the adrenergic vascular response. Isoproterenol modifies the response to norepinephrine and also to vasopressin [101].

Imprinting of paths of heterodifferentiation can be also induced by hormones of similar molecular structure although their action is different. For instance, perinatal exposure to oxytocin determine a persistent hypersensitivity to vasopressin [97]. The use of oxytocin to induce delivery will have to be re-evaluated in view of these findings.

Imprinting of paths of heterodifferentiation by polluting agents displaying hormonal action

Several estrogens, androgens and progestins are still widely used as farm animal or bird growth promoters in several countries, mainly in the Third World, without any efficient control from the Authorities [70, 72, 73]. Diethylstilbestrol is one of the reported hormones used at least recently [70, 72]. Very high estrogen levels were detected in chicken and beef meat in Puerto Rico [71]. Epidemics of premature telarche, gynecomastia, other signs of precocious sexual development, ovarian or uterine enlargement, ovarian cysts and increased estrogen levels in the blood were reported in children of several countries [71, 74, 102], caused by exogenous estrogen contamination in the food ingested by the children and by their mothers [71].

The high incidence of premature telarche reflects the action of high levels of hormones, that may imprint paths of heterodifferentiation in prenatally or postnatally exposed population, determining increased incidence of diseases as gynecological malignancies, infertility, immune deficiencies or autoimmune diseases. Further, it may determine character and behavioral alterations, including changes sex-dimorphic behavior, sexual orientation (homosexuality), or even development of violent behavior. If hormone contamination in food is high enough to determine some of the behavioral alterations in part of the population, it may present important social repercussions. The risk of exposure to very high hormone doses from food exists indeed, since hormones are sometimes implanted in eatable parts of the animal, or cattle is killed sometimes shortly after implantation.

Imprinting of paths of heterodifferentiation by pharmaceuticals, polluting agents or other non-hormonal substances.

The imprinting of paths of differentiation is not an exclusive attribute of hormones. Non hormonal molecules interacting with hormone receptors or other equivalent structures may also induce this phenomenon, as shown with sugar molecules glucosamine and mannose, that alter the reactivity of pancreatic beta cells in rats and the production of insulin in adults [103]. Various pharmaceuticals, polluting agents, ethanol, drug abuse agents, food additives, and even some substances normally present in some foods were also incorporated into the list of agents capable of imprinting paths of heterodifferentiation (*vide infra*). Every day more compounds are described as sharing this characteristic; perhaps, in the years to come, several currently considered innocuous compounds will increase the list. Below are described a few examples.

Diazepam and related pharmaceuticals

Besides its medical use, it is frequently used in many countries by self-prescription and as a substance of abuse. Prenatal exposure to diazepam of experimental animals permanently decreases ß-adrenergic receptors in brain cortex, striatum and hypothalamus, but not in the cerebellum [104], alters dopaminergic function in some brain areas [105] and changes the low affinity form of the GABAA receptors [106].

The biochemical changes in the differentiation of the cell-types affected by diazepine may explain changes the ability to cope with stress [105], in adult behavior [105] including motivational responsiveness to environmental challenges [107], in the copulatory activity of male rats [107] and the severe depression in the cellular immune response [108].

Phenobarbital

It is widely used in the treatment of epilepsy. Its prenatal exposure induces an important decrease in dendritic development of rat hippocampus neurons during the first postnatal month [109]; causes feminine sex behavior in adult male hamsters [110] and reproductive dysfunctions in the male rat, in-cluding delay in testis descent, decrease in seminal vesicle weight and fertility reduction [111]; it elicits puberty delay, aberrant cycles, infertility, increases in estrogen levels in the blood and estrogen receptors in the uterus in female rats. In humans, it presents a negative effect on cognitive development [112].

Ethanol

Its prenatal exposure from maternal alcohol intake during pregnancy, mainly affects the central nervous system. In the rat causes a decrease in the thickness of brain cortex and changes in glucose metabolism in certain brain areas, mainly affecting neurons from the thalamus and corpus callosum connections [113]. It causes permanent changes in brain benzodiazepine [114] and serotonergic 5-HT1 [115] receptors as well as a change in enkephalin level [116] and norepinephrine secretion destabilization [117]. It induces a change in astrocyte enzymes which may cause neuronal alterations [118], a decrease in the number of neurons [119], morphological changes in neurons [110, 120], and impairment in the development of hippocampus pyramidal cell dendrites [121].

The above changes may be the biochemical and morphological substratum of the behavioral changes observed after prenatal exposure to ethanol [114], among

which is important to mention an increase in aggressivity [122]. Prenatal exposure also determines permanent immunologic depression [123], alteration in sex dimorphic behavior [124] and reproductive changes such as a decrease in hypothalamic sensitivity to testosterone feedback [125], increase in fetal testosterone levels and estrus cycles disruption [126].

Nicotine

In the rat, prenatal exposure to nicotine causes an increase in spontaneous locomotor activity [127], that can be explained by the changes in striatum dopamine binding sites [128]. It causes persistent alterations in the functional state of catecholaminergic neurons, evidenced by a persistent decrease in MOPEG and, in male rats only, an increase in noradrenaline content [129]. It elicits up-regulation of adenylate cyclase activity in membrane preparations of kidney and heart, not accompanied by ß-adrenergic receptor up-regulation, that can be explained by changes in enzymes involved in membrane receptor signal transduction, leading to altered responsiveness independently of changes at the receptor level [130].

Prenatal exposure to nicotine also alters subsequent sexual behavior in males, increasing the latency before the physiological changes that occur during intercourse and decreasing the efficiency of the copulation [131]. These alterations may be caused by the decrease in blood testosterone levels observed in adult prenatally exposed animals, due to a decrease in hormone synthesis in the testis [131].

Pesticides

Prenatal exposure to polychlorobiphenyl pesticides causes persistent behavioral changes in rats [132]. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) elicits thymus gland atrophy and immune suppression [133], through an alteration in the path of differentiation of lymphocyte stem cells [133].

Lead

In the rat, prenatal exposure to lead causes a permanent increase in the affinity of Ù- but not µ-opioid receptors in the rat brain [134], that parallels the impairment of opioid but not non-opioid stress-induced antinociception in developing rats [135]. If these changes also occur in humans, they may explain behavior changes that occur in exposed population [136-138], and perhaps may explain increased frequency of addiction to opioid or other abuse drugs in high lead contaminated environments (*vide infra*). The finding that the dopa-mine and 5-hydroxyindoleacetic acid response to amphetamine is en-hanced in lead-exposed animals [139], suggests that the response to other stimulant abuse substances may be enhanced as well.

In experimental animals, exposure to lead impairs learning [140]. In humans, it causes deficits in central nervous system functioning that persists into adulthood, including learning impairment, deficit in psychometric intelligence scores, lower IQ scores, poorer school performance, increased school failure, reading disabilities and poorer eye-hand coordination [136-138]. Imprinting of paths of heterodifferentiation in central nervous system cells may explain these alterations at least in part.

Exposure to lead also affects the reproductive system. In perinatally exposed adult rats, the number and characteristics of uterine estrogen receptors differs from that of non-exposed animals [141]. A permanent alteration of ovary gonadotropin receptors and of steroidogenesis has been detected under the effect of the exposure [142]. These alterations explain, at least in part, the known depress in fertility in lead exposed experimental animals [143] and humans [144]; they support the hypothesis that lead intoxication caused the fall of the Roman Empire due to infertility of the ruling class (*vide infra*) [145].

Natural food components and additives

Natural foods components may imprint paths of heterodifferentiation. In experimental animals, sugar molecules such as glucosamine and mannose may alter the reactivity of pancreatic beta cells insulin production during adulthood [103], high perinatal dietary fat feeding alters hepatic drug metabolism during adulthood [146] and induces a cholesterol homeostatic memory [147], high perinatal NaCl diet determines in the adult increases in NaCl intake and sodium excretion [148]. This suggests that dietary factors in early life modify the extent of adaptative responses in adult life [147].

Some foods or beverages contain active agents. For instance, coffee, besides caffeine, also contains estrogenic agents [149] that may imprint paths of heterodifferentiation (*vide supra*). Prenatal caffeine determine in the adult rat increased activity and decreased emotionality; higher doses of caffeine may have the opposite effects [150]. Exposure to pregnant rats to caffeine inhibits differentiation of testis interstitial tissue and Leydig cells and reduces testosterone synthesis by fetal testis [151], which may in turn imprint paths of heterodifferentiation in other tissues.

Many processed foods and beverages contain exogenous compounds that may imprint paths of heterodifferentiation. For instance, caffeine is added to some soft drinks in several countries and pregnant women are usually not warned about it. Nitrates or nitrites, added to foods, may cause discrimination learning deficit and impaired retention behavior following prenatal exposure [152]. In some countries, tetracyclins are added to frozen food [70]; prenatal exposure to this antibiotic causes persistent immune deficits [153, 154]. Many food color additives and other substances used to improve organoleptic properties of food have not been yet evaluated for health risks following perinatal exposure.

Prenatal stress

Prenatal exposure to maternal stress alters morphine- and stress-induced analgesia in male and female rats [155]. This may be explained by persistent decrease in µ-opioid

receptors in the striatum but not in other brain regions in prenatally exposed adult rats [156]. Prenatal stress also affects adult sex behavior both in experimental animals and in humans. In rats, it feminizes and demasculinizes male behavior [157]. In humans, it increases homosexuality in males [158].

Stress may interact via hypersecretion of various maternal hormones, which in turn cause sex behavior changes imprinting paths of cell heterodifferentiation.

Possible wider effects of imprinting of paths of heterodifferentiation

We proposed (*vide supra*) that prenatal or early postnatal exposure to lead imprints paths of cell heterodifferentiation in various organs, causing changes in their receptors and alteration in their responsiveness to hormones, neurotransmitters or exogenous substances. In the uterus, ovary and perhaps hypothalamus, these changes lead to an alteration in the reproductive capacity of exposed population. Changes in estrogen and perhaps opiate receptors in the central nervous system lead to alterations in sex behavior and sexual orientations. In the brain, other biochemical changes may cause neurobehavioral and psychopathic alterations. The increase in affinity of brain opiate receptors and increase in sensitivity for endogenous or exogenous opioids, may favour a tendency toward addiction to morphine-like narcotics or indirectly, to cocaine or amphetamine stimulants.

If, therefore, a significant part of a population is neonatally exposed to lead, it is possible to expect an increase in the incidence of infertility, sex behavior alterations, homosexuality, addiction to drugs of abuse, criminality and other kinds of antisocial behavior [159]. This may contribute to a decadence of an exposed society, its cultural decline, disorganization and finally disappearance.

In this context, the fall of Rome was related to the wide use of lead in water conveying, wine and fruit juice storage vats, and paints. Gilfillan [145] suggested that the declining birth rate and apparent increased incidence of psychosis in Rome's ruling class, which may have been at the root of the Empire's dissolution, were a result of exposure to lead in food and wine [145]. Recent reports on estrogen, gonadotropin and opiate receptors, may explain the increase in the incidence of infertility, homosexuality (the known Roman Bacchanalian orgies) and the apparent addiction to narcotic plants in the Roman population, as well as their incapacity for defense against foreign invaders.

The second part of the present century has seen an important epidemic of addiction to drugs of abuse has developed, first, in large cities from the U.S.A., then, in large cities from Western Europe, and currently it has started to develop in most large cities from South America. It did not affect rural or small town population localized far from large cities. This addiction to nar-cotic or stimulant drugs parallels a simultaneous increase in criminality and an apparent increase in the incidence of alterations in sexual orientation.

According to our hypothesis, these changes can be explained, at least in part, by an important increase in lead pollution in large cities, but not in small towns, that appeared first in North American, then in Western European and subsequently in South American cities, caused by an increase in the use of leaded gasoline. Perinatal exposure to lead would have originated changes in brain opiate, estrogen and other receptors and subsequent neurobehavioral alterations.

The populations of several countries may also be exposed to other pollutants, such as hormonally active compounds from the meat of farm animals or poultry treated for anabolic purposes; color and other additives in foods or beverages; pesticides, nicotine, ethanol and substances of abuse. In addition, the population may be exposed to natural products in ceertain food products preferentially ingested in these countries.

The effects of some of these agents are currently well known, but the possibility of imprinting of routes of heterodifferentiation by the remaining substances have not been yet investigated. It is possible that many of ancient and perhaps more recent civilizations declined due to exposure to some of these agents, especially those that impair intelligence or cause psychological changes affecting the society.

Perspectives and conclusions

Many health conditions in a community, such as the incidence of various diseases and its behavioral and psychologic characteristics, are in part determined by agents to which people are exposed during prenatal or early postnatal life. It was already suggested that the focal prevalence of human diseases has social and ecological causes, i.e., is determined by environmental and cultural factors of any society [160]. In agreement with this proposal, the fetal and infant origins of adult diseases was pointed out [161].

Therefore, single individuals or most individuals from any human community can be exposed, during prenatal or early postnatal age, to different agents or conditions changing the paths of differentiation of different cell-types, determining their health conditions, behavioral characters and mental abilities. Although these characteristics may be sometimes convenient, they most probably are adverse, if they favor an increased incidence of diseases such as immune depression, cancer, infertility, psychological changes or neurobehavioral alterations. Perhaps the behavioral characteristics of any ethnical group or society are determined, at least in part, by their food preferences or by local pollutants.

This new field in the Medical Sciences may display great importance in the Medicine of the future. When the diseases that develop following prenatal or neonatal exposures will be identified, and when most of the potentially harmful agents imprinting paths of

heterodifferentiation will be recognized, we will be able to avoid these agents or neutralize their effects. Much research and a strong will to avoid exposure to toxic agents are therefore necessary to achieve a substantial improvement of health conditions for mankind.

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