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# The Hygiene Hypothesis and the Participation of Chemical Products

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**Abstract**

Hygiene hypothesis as a cause of adult diseases emerged in 1989 by David Strachmann. Since then controversial studies have been published and recently the importance of the microbiome in the rapidly increasing prevalence of some diseases is established. Microbiome is considered the symbiotic group of pathogens within mammals that consists from the bacteria of epidermis, gastrointestinal and respiratory tract. The concept of the 'exposome' is a broader term to include not only symbiotic pathogens, but a great variety of exogenous and endogenous chemicals in one's lifetime. Exogenous exposures include environmental chemicals, whereas endogenous are formed from different metabolic processes. The long term toxic results of these chemicals are due to epigenetic modifications of the genome with greatly unknown consequences.

**Keywords:** Hygiene; Chemical products; Microbiome

## Introduction

Hygiene hypothesis was introduced by David Strachmann in 1989, who detected an inverse relation between the number of children in a family and the incidence of an allergic disease [1]. He concluded that the key point was the number of infections during infancy and early childhood which determined a specific phenotype towards allergy. The hypothesis was investigated the following years with controversial results [2]. It became clear that infections of the gastrointestinal tract, especially infections from helminthes and early exposure to endotoxin had a protective effect from allergy, unlike respiratory infections, especially from respiratory syncitial virus and rhinovirus, that contribute to the development of asthma. Studies on the underlying immunological mechanisms showed that allergic children had a skew of the immunologic response towards TH2 response [2].

Subsequently, research was focused on pathogens that colonize the mucous membranes and epidermis as an early exposure to mild pathogens that educate the immature immune system. The pathogens are known as microbiome and include pathogens colonizing the gastrointestinal and respiratory tract as well as pathogens colonizing epidermis [3]. Colonization of the lumen with Lactobacilli was statistically significant in children without an allergic disease, whereas colonization with Clostridia, Coliforms and Staphylococcus aureus was more frequent in children with allergies.

The matured hygiene hypothesis suggests that the complex interaction of a framework of genetically determined pattern recognition receptors (PRRs) of the innate immunity with the variety of pathogens of the symbiotic microbiome is responsible for the education of the immune system the early years of life. The development of balanced TH1/TH2 responses and regulatory mechanisms of adaptive immunity is established. Therefore, the imbalance of these responses could probably cause allergic and autoimmune phenomena. These findings display another parameter to the development of disease besides the genetic component, which suggests that environmental factors have a strong contribution. Furthermore, a broader set of agents, including those to which the individual is exposed to, at the home, at schools, in the daycare, etc other than pathogens could contribute to immunomodulation [4].

The concept of the 'exposome' is a broader term to include not only symbiotic pathogens, but a great variety of exogenous and endogenous chemicals in one's lifetime. Exogenous exposures include environmental chemicals, whereas endogenous are formed from normal metabolism, inflammation, oxidative stress, lipid peroxidation, infections, and other natural metabolic processes. Chemicals induce oxidative stress to the cell and the production of free radicals. These radicals urge epigenetic modifications on the genome with unpredictable consequences [5].

## Industry chemicals [6]

The early 19th century in western societies is characterized by the evolution of industry and a modern lifestyle. Increasing data show that westernized societies are exposed to a variety of industrial products through diet, water and air pollution in toxic levels. Most of these interfere with DNA sequence and cause deleterious mutations and in addition modify epigenetic marks that predispose to disease. Investigations have identified several classes of environmental chemicals that modify epigenetic marks, including metals (cadmium, arsenic, nickel, chromium, and methylmercury), peroxisome proliferators (trichloroethylene, dichloroacetic acid, and TCA), air pollutants (particulate matter, black carbon, and benzene), and endocrine-disrupting toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants and dioxin).

Metal-induced oxidative stress is a unifying process to account for intoxication from different metals. Metals are known to increase production of reactive oxygen species (ROS) in a catalytic fashion via redox cycling. ROS are responsible for DNA damage and interfere with the ability of methyltransferases to interact with DNA, thus resulting in a generalized altered methylation of cytosine residues at CpG sites. The most frequent consequence of such alterations is mutagenesis and hypomethylation that are considered responsible for the evolution of cancer.

Specifically, cadmium has a low potential of carcinogenesis and causes hypomethylation due to inhibition of DNA methyltransferase binding domain. Chronic exposure to inorganic arsenic reduces methyl availability to methyltransferases and relates to changes in miRNA expression that is partly reversible by folate. The mechanisms underlying nickel health-related effects, including carcinogenicity and cardiorespiratory disease, are still largely unknown. It has been proposed that nickel may replace magnesium in DNA interactions. Chromate exposure predisposes to lung cancer through hypermethylation of p16 and alterations of various histones.

Methylmercury is an environmental contaminant and a potential neurotoxic agent that may be present at high levels in seafood. Perinatal exposure to methylmercury causes persistent changes in learning and motivational behavior in mice. Exposure to low levels of methylmercury during development induces epigenetic suppression of brain-derived neurotrophic factor (BDNF) gene expression in the hippocampus and predisposes mice to depression. Trichloroethylene (TCE), dichloro acetic acid (DCA), and TCA are environmental contaminants that contribute to the hypomethylation of the promoter regions of myc genes by depleting the availability of methyl residues.

### Air pollution [6]

Air pollutants that interfere with the homeostasis and predispose to cardiovascular morbidity and lung cancer are the particular matter, carbon, benzene exposure and hexahydro-1, 3, 5-trinitro-1, 3, 5-triazine (RDX). Global hypomethylation, as investigated in Alu- and LINE-1 repeated sequences, as well as gene specific hypermethylation is frequently detected to people exposed to these materials. In addition, high risk of acute myelogenous leukemia is a feature of prolonged exposure to benzene and neurotoxicity and immunotoxicity a feature of prolonged RDX exposure.

### Endocrine-disrupting chemicals [7]

An endocrine-disrupting compound is defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process". Some chemicals with these properties are PCBs, industrial solvents, plastics and plasticizers and pesticides/fungicides. They exist in every day products and/or contaminate soil and water and reach the top of the food chain, thus humans. Their use is wide spread and they have long half-life in the environment. These chemicals accumulate in human adipose tissue and express their properties when a toxic level is reached.

Their toxic effects depend on the age they are consumed, the latency and usually there is an undetectable lag between exposure and manifestation of a disorder. The use of various -probably unknown- chemicals that act as endocrine disruptors and their mixtures make them to have unpredictable dose-response dynamics. The knowledge that they are responsible for epigenetic alterations has emerged recently.

As far as the reproduction system is concerned, they are responsible for cryptorchidism, hypospadias, oligospermia, prostate hyperplasia and testicular cancer in males, a syndrome known as testicular dysgenesis syndrome (TDS). In the female, they seem responsible for premature thelarche, uncommon vaginal adenocarcinoma and pathogenesis of several female reproductive disorders, premature ovarian failure, polycystic ovarian syndrome, aneuploidy, reproductive tract anomalies, uterine fibroids, endometriosis, and ectopic gestation. Because they interfere with the endocrine system as a whole, their properties expand to all the developing tissues, including the central nervous system. Their impact on the thyroid function, influences metabolism and causes obesity, and cardiovascular problems. Nevertheless, they become a serious concern for public health.

Diethylstilbestrol (DES) is an estrogen used to prevent miscarriages during pregnancy. Carcinogenesis of teenage girls that have received the medicine as embryos was detected. Research studies found that this medicine inhibites catechol-O-methyltransferase (COMT) gene transcription and thus prevents normal methylation processes. Bisphenol A (BPA) is another chemical with estrogenic properties that is present in many commonly used products including food and beverage containers, baby bottles, and dental composites. It alters methylation status when is provided in toxic levels during pregnancy and early childhood. Dichloro-diphenyl-trichloroethane (DDT), dichloro-diphenyl-dichloroethylene (DDE), b-benzenehexachloride (b-BHC), oxychlordane, a-chlordane, several polychlorinated biphenyls (PCBs), and dioxin share same properties.

### Antibiotics

Antibiotics were discovered in the early 20th century and their use became widespread after 2nd World War [8]. The advantage of preventing and eradicating various infectious diseases is counterbalanced by the consequences of overuse of antibiotics, mainly resistance and interference with immune maturation the first years of life. The use of antibiotics in infancy and early childhood is expanding worldwide. In the US, it is reported that the average child has at least one antibiotic course per year [9].

Another emerging problem is the use of antibiotics in low doses in agricultural industry since the 1950s [10]. These drugs given in low doses with food or water promote growth of farm animals and increase weight by 15%. Classes of antibiotics usually used are macrolides, tetracyclines and penicillins. However, the use of antimicrobial agents of different classes alters the population structure of the gut microbiome of the animals as well as its metabolic capabilities. The gastrointestinal tract contains an exceptionally complex and dense microbial environment which we know that is responsible for the maturation of the immune responses and stimulates a rich spectrum of mechanisms involved in innate and adaptive immune responses. It is also an area of hormone production, including those involved in energy homeostasis (such as insulin, glucagon, leptin and ghrelin) and growth. Alterations of the microbiome modify many host metabolic, hormonal and immune homeostatic processes. These changes have a secondary impact on humans who consume the animals' products.

## Discussion

Hygiene hypothesis as a cause of adult diseases emerged at 1989 with David Strachmann. In its simple form it was born to connect infections of early childhood with allergic rhinitis. Controversies of scientific studies matured the hypothesis to a more complex one that enlightens the fact that not all infections have similar effects. Generally speaking, research put up different results and it is though that gastrointestinal infections promote the maturation of immune system, while respiratory contribute to asthma. Besides, elminthes –our counterpart friends in evolution- offer an advantage against inflammation.

Recently, scientists have focused on the importance of the so called 'microbiome'. Microbiome is considered the symbiotic group of pathogens within mammalians and it consists of bacteria colonizing epidermis, gastrointestinal and respiratory tract. The aberrant lymphatic tissue that surrounds these tissues is highly developed and precedes a huge number of antigenic signals. This process is a main feature of the development of immune tolerance. Dysfunction of the process is the cause of various inflammatory diseases. Abnormal maturation of the innate and adaptive immunity in infancy and early childhood is implicated in the appearance of allergic and autoimmune diseases in adulthood, including diabetes mellitus and probably is responsible for the development of neurodegenerative disorders such as autism and Alzheimer disease.

The rapidly increasing prevalence of these diseases in westernized countries is an issue of major health concern. Research has focused to the causes of alteration of microbiome and the mechanisms emerging these diseases. Our knowledge of them could offer new more effective therapeutic options and in addition measures for their prevention.

The causes of the alteration of microbiome in modern societies are yet obscure. Dietary products are a major concern, but the expansion of the issue is beyond this review. Scientists are greatly concerned about the effects of chemicals that flood the environment. Chemicals used for food preservation, infrastructure, every day facilities and more over in the agriculture industry such as insecticides and antibiotics have an unpredictable and unknown impact in public health. Pollution by industry byproducts, air pollution by organic chemicals and other pollutants cause serious health problems. These substances are in the environment of the modern man and interfere with the microbiome as well with different functions of the human body.

Research indicates that the mechanism of toxic alterations is oxidative stress and epigenetic alterations, mainly DNA methylation. Epigenetic modifications are found in diseases such as cancer, allergy and others of which prevalence rapidly increases. Scientists start to observe the epigenetic effects in various multifactorial diseases where the significance of the environment has a central role. Another aspect is that, epigenetic alterations are known to be heritable with major consequences for the following generations.

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