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ORIGINAL PAPER

Is there scientific evidence that suppression of acute diseases in childhood induce chronic diseases in the future?

MZ Teixeira[1]*

[1]*Department of Clinical Medicine, Faculty of Medicine, Universidade de São Paulo, São Paulo, Brazil*

Seeking to understand the individual in his symptomatic totality has been an aim of homeopathy since its beginning. Even then there were warnings that inadequate treatment of acute diseases in childhood may lead to future chronic diseases. Hahnemann cautioned that by treating acute diseases with allopathic medicine, with strong doses of heroic drugs, or suppressing local symptoms of those diseases, would increase the risk of future chronic diseases. Burnett proposed the theory of vaccinosis and warned of chronic manifestations subsequent to smallpox vaccination. French homeopaths, seeking the physiopathological origin of chronic diseases, correlated it to the abnormal reaction of the reticuloendothelial system (RES). Through the study of experimental pathology, Maffei attributed symptomatic manifestations to the imbalance between the immunological phenomena of allergy and immunity. He termed the sensitizing and pathogenic effects of medications and vaccines, 'metallergy' and 'parallergy', respectively.

The hygiene hypothesis is based on evidence that the imbalance of immunological response in childhood, specifically among the Th1 and Th2 lymphocyte subpopulations, is responsible for the development of some allergic and chronic diseases in the future. The deranging factor for the predisposition to future allergic response (Th2) is the obstruction of natural manifestations of infectious diseases (Th1 response) in young children. Homeopathic treatment aims to equilibrate vital reaction, corresponding to an integrative physiological response, it may regulate Th1/Th2 imbalance. However, clinical trials to support this hypothesis are lacking. *Homeopathy* (2002) **91,** 00–00.

Keywords: vaccination; immunization; vaccinosis; hygiene hypothesis; chronic diseases; acute diseases suppression

Introduction

The clinical model of homeopathy is based on the minute observation of individual symptoms (symptomatic totality), in the study of the curative properties of drugs (experimentation on healthy individuals), the application of a therapeutic method (similitude principle), and the evaluation of patient follow-up (homeopathic prognosis). Its aim is to understand the diseased individual in a global and dynamic manner, observing organic disorders which go unnoticed by the less attentive observer. Since the very beginning of homeopathy, there have been reports by homeopathic physicians who observed, in clinical practice, the occurrence or recurrence of chronic diseases after inadequate treatment of acute diseases. This may be due to the use of drugs, creams or ointments to eliminate local and external symptoms, the indiscriminate use of allopathic medicine, etc.

*Correspondence: Marcus Zulian Teixeira, R. Teodoro Sampaio, 352 - cj. 128, São Paulo/SP - CEP 05406-000 Brazil.
E-mail: marcus@homeozulian.med.br
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For Hahnemann, these incidents resulted in an imbalance of the organism's vital reaction. The French homeopathic school called this imbalance of vital energy 'reticuloendotheliosis', attributing chronic diseases to the abnormal reaction of the reticuloendothelial system (RES) to external aggression. Further fueling the controversy there are frequent references by homeopaths to the occurrence of allergic and atopic diseases in children after immunization. Maffei relates the origin of chronic diseases to the distorted or altered reaction of the RES to antigens, resulting from the imbalance between immunity and allergy, terming diseases secondary to medicinal and vaccinal stimuli in 'metallergy' and 'parallergy', respectively.

The current 'hygiene hypothesis', which seeks to explain the rise in allergic and chronic diseases the throughout developed countries over the last decades, provides scientific evidence to support the episodes cited by homeopaths. It identifies the cause of such phenomena as the imbalance of lymphocytic immunological response, secondary to the inhibition of manifestations of childhood infectious diseases. There is misinterpretation by both homeopathic and non-homeopathic physicians. Some homeopaths fail to remember the idiosyncratic manner in which each organism reacts. On the other hand, some non-homeopaths ignore evidence seen in clinical practice and fail to believe the potential risks of certain therapeutic practices reported in many scientific studies. This paper aims at basing a number of the empirical observations by homeopathic physicians in modern scientific studies.

Homeopathic hypothesis: acute diseases *vs* chronic diseases

Throughout the two centuries of homeopathy's existence, homeopathic doctors have observed and evaluated human individuality and symptomatic totality. They relate the occurrence or reoccurrence of chronic diseases to inadequate development of acute diseases and excessive curative or prophylactic treatments as the source of this imbalance. They observed that different chronic diseases were the result of the organism's abnormal reaction to morbific agents and, through various reactive forms, sought the physiopathological foundation for the homeopathic theory of miasms.

In paragraph 11 of the *Organon of Medicine*,[1] Hahnemann attributed any adverse sensation, function or symptom, to an abnormal reaction of the organic vitality to a morbific agent: '[...] it is only the vital principle, derange such an abnormal state, that can furnish the organism with its disagreeable sensations, and incline it to the irregular processes which we call disease; [...]'.

In paragraphs 72–78 of the *Organon,* he discusses the subject of this study. In paragraph 72, he divides human diseases into two types. The acute diseases 'are rapid morbid processes of the abnormally derange vital force, which have a tendency to finish their course more or less quickly, but always in a moderate time.' Chronic diseases are those that affect the organism unable to satisfactorily defend itself with disease spreading and becoming more and more abnormal 'until at length the organism is destroyed'.

Among acute diseases, he cites acute fevers that occur secondarily to the 'exciting and injurious cause' (food-borne, climatic, meteorological, toxic, occupational, psychic, etc) or the contagious 'acute miasma'. As an example of the acute miasmas that always reappear in the same manner, he cites small pox, measles, whooping cough, etc (Section 73).

Chronic disease, originating from dynamic infection by a 'chronic miasm' *(psora, sycosis* and *syphilis),* can be 'artificially produced in allopathic treatment by the prolonged use of violent heroic medicines in large and increasing doses, [...] whereby the vital energy is sometimes weakened to an unmerciful extent, sometimes, if it does not succumb, is gradually deranged (by each substance in a peculiar manner) in such a way that, in order to maintain life against these inimical and destructive attacks, it must produce a revolution in the organism, and either deprive some part of its irritability and sensibility, or exalt these to an excessive degree, cause dilatation or contraction, relaxation or induration or even total destruction of certain parts, and develop faulty organic alterations here and there in the interior or the exterior (cripple the body internally or externally), in order to preserve the organism from complete destruction of life by the ever-renewed, hostile assaults of such destructive forces'. (Section 74).

He also cites a number of reports in which a more virulent acute disease is able to temporarily improve a less virulent pre-existing chronic disease (Section 38).

In paragraphs 185–203 of the *Organon,* he criticizes topical and external treatments that aim to suppress external symptoms of the 'local diseases', due to risk of changing an 'acute local infection' into a 'manifested chronic disease', or of later worsening and intensifying an internal miasmatic disease. He distinguishes the 'ailments and diseases that depend on a persistent unhealthy mode of living, as also those innumerable medicinal maladies caused by the irrational, persistent, harassing and pernicious treatment of diseases often only of trivial character' from the greater number of natural chronic diseases, resulting from the development of the three chronic miasms (*psora, sycosis* and *syphilis*). He states that the main cause of the great development of chronic disease is the partial and suppressive treatment of these chronic miasmas with the aim of only eradicating 'the local substitutive symptoms that quell the general internal illness'. These chronic diseases would have remained latent if 'local remedies for their corresponding external symptoms' had not been used. (Section 204).

In relation to vaccination or immunization, which some homeopaths claim to be the cause of allergic and chronic diseases, Hahnemann was a contemporary of Edward Jenner (both published their first essays in 1796) and praised Jenner's discovery as a form of 'homeopathic' therapy, using a 'similar' antigen in the prophylactic treatment of human smallpox: '[...] Universal vaccination put an end to all epidemics of that deadly fearful smallpox to such an extent that the present generation does no longer possess a clear conception of the former frightful smallpox plague' (Section 56, footnote). In *The Chronic Diseases*,[2] Hahnemann characterized the three chronic miasms as different ways the organism reacts with specific symptoms and outbreaks (*psora:* scabies, eczema, pruritus, etc; *sycosis:* polyps, warts, chronic catarrh, etc; *syphilis:* ulcers, cankers, necrosis, etc). He also criticized the use of local homeopathic medication aimed at only treating superficial symptoms of acute inflammatory diseases, with no concern for treatment of symptomatic totality with miasmatic or *antipsoric* medications.

In 1890 James Compton Burnett,[3] an English homeopathic physician, described the symptoms of morbid disturbances of 'extreme chronicity', following smallpox vaccination. They included neuralgia, neuritis, chronic cephalea, boils, asmathiform bronchitis, etc. He related these imbalances to the symptoms described by Hahnemann in his discussion of the chronic miasm 'sycosis'. Burnett referred this group of organic disorders he observed subsequent to smallpox vaccination as 'vaccinosis'. He developed the concept that by suppressing acute disease, vaccines can subsequently induce chronic diseases, with predominantly allergic symptoms (dermatitis, rhinitis, sinusitis, bronchitis, etc).

In the mid-20th century, following other French homeopaths (Grauvogl, Martiny, Fortier-Bernoville, Martiny, Zissu), Henri Bernard[4,5] related Hahnemann's chronic miasma to the ways the organism reacts to the 'toxins', regardless of individual constitution. Using Hans Seyle's[6] theory of 'General Adaptation Syndrome to Stress', which defines any disease as 'a reaction of the entire organism to aggression', Bernard attributed the genesis of chronic disease (sclerosis) to abnormal reactions of the RES to external aggression. In the Sulphuric Constitution (psora), the organism responds with a swift and intense defence reaction (acute inflammation), capable of eliminating harmful agents from the organism, protecting tissue from the accumulation of metabolites which are responsible for the chronicization of disease. In the Carbonic Constitution (sycosis), the delay in the RES's reaction blocks the normal toxin elimination mechanism, promoting a build-up of 'sycotic deposits' in the tissues, subsequently triggering the manifestation of 'chronic reticuloendotheliosis' or 'sclerosis' (slow and progressive toxic aggression to the RES): 'hydric imbibition of tissues, chronic secretion of mucous membranes, proliferation of benign cells, slow and torpid organic reactions, sclerogenic tendency and depression of nervous system'. Causes of this state, according to these authors, include steroids and vaccines. In the Phosphoric (or fluoric) Constitution, corresponding to the syphilitic chronic miasm, the RES's defense reaction is ineffective and chaotic, allowing a massive and disorganized attack of the harmful agents without successful elimination, triggering chronic irritation, ulceration and sclerosis.

According to Husemann and Wolff,[7] proponents of anthropsophic medicine, there is a polarity between acute and chronic diseases and between inflammation (fever) and sclerosis (calculosis, diabetes, and cancer). They emphasize that 'every suppression of a fever or inflammation tilts the balance in favour of a disease tending towards sclerosis', and 'people who do not go through childhood diseases present a greater tendency for cancer'. They cite study results with cancer patients in Germany where, in retrospective analysis, low rates of inflammation are evident. 'In cases of clear 'inflammatory diathesis' the occurrence of a cancerous affliction was rare. [...] the constitution, through infectious diseases, undergoes a transformation that considerably reduces disposition to carcinoma'.

In a study on vaccinations, Brito and Spozatti[8] argue against the 'negative' points of vaccination, stating that 'there are no studies with scientific consistency in homeopathic literature that support the negative points brought up by some authors'. Just negative points include the following claims: vaccinations induce allergic manifestation in airways and on the skin; vaccinations can induce depression of the immunological system; vaccinations alter a child's vitality; vaccines for tuberculosis and measles are only indicated for malnourished children and are unnecessary for healthy children; side effects of vaccines are serious and it would be better if the child had the disease and then received homeopathic treatment. Similarly, they warn of the lack of scientific investigation in 'the use of nosodes as immunoprophylactic agents' and in 'the use of homeopathic medication or dynamized vaccines in greater strengths as a preventative and/or therapeutic measure to conventional vaccines'. Emphasizing the official stand of the Brazilian Homeopathic Medical Association which supports the National Immunization Program, the authors encourage homeopathic researchers to seek out scientific proof of the empirical observations cited by homeopathic physicians.

Hypothesis of experimental pathology: immunity *vs* allergy

Walter Edgard Maffei, former professor of General and Special Pathology at the University of São Paulo Medical School, in his book *Os Fundamentos da*

Medicina,[9] defines disease as 'the group of functional and organic alterations, of evolutionary character, which appears in an individual affected by an external agent, against which his organism reacts'. Dividing defence mechanisms according to their cellular or humoral natures, he emphasizes humoral or acquired immunity, active or passive, as a result of the antibodies produced by RES according to antigenic sensitization, the genotype, age and state of nutrition. When this immunity process fails, allergy phenomena occur, the result of the antigen–antibody interaction in the tissues. This results in manifestations, variable between individuals, following an alteration or disturbance in the organism's reaction which constitute allergy (gr., *allos* = other + *ergon* = strength, energy).

In 1905, Clemens von Pirquet[10] introduced the following concept: 'allergy represents all of medicine, because any sickness or simple symptom represents an altered reaction of the organism'. Allergy results from 'the specific antigen–antibody shock that takes place in tissues', manifesting characteristic symptoms and anatomic-clinical symptoms. Immunity consists in 'the specific antigen–antibody shock that takes place in the humors', with tissues remaining unaffected, showing neither symptoms or anatomic-pathological disturbances. As these phenomena are opposites, the balance between them is responsible for the 'state of health': when allergy predominates, immunity is low and, inversely, when immunity prevails, allergy is low.

Maffei classifies altered reactions according to intensity, duration, sensitizing dose and the triggering cause: hyperergy, hypoergy, anergy, parallergy and metallergy. 'Hyperergy is an intense, violent reaction, indicating maximum antibody attack–response against the antigen with the aim of locating and destroying it in a determined location'. It corresponds to the Koch and Arthus phenomena, with a violent inflammatory process, intense congestion, oedema and subsequent necrosis. After complete destruction of the antigen, immunity occurs. 'Hypoergy is a more attenuated reaction not only in its clinical manifestation, but also in its anatomic-pathological manifestations, for example, a chronic inflammation'.

'Anergy is the organism's failure to react, meaning a lack of antibody production, which can be either positive or negative'. In positive anergy there is the resolution or cure of illness after an initial hyperergic reaction in which antibodies neutralize the antigens. Tissue allergy disappears and humoral immunity prevails (eg lobar pneumonia). On the contrary, in negative anergy 'the organism is unable to produce any more antibodies as it has exhausted its capacity to react and, consequently, to defend itself. There is no longer allergy nor immunity; there is a deterioration and death' (eg chronic tuberculosis). In anergy, antibody production is interrupted without antigen–antibody shock in tissues, characterized by the lack of a reaction and the absence of symptoms.

Parallergy (gr., *para* = abnormal functionally + *allergon*) corresponds to the non-specific antigen–antibody shock, 'the most important defence mechanism of human pathology, since in it allergy as such does not exist'. This non-specific sensitization begins *in utero* and takes place through 'all the normal childhood infections, from common throat infections to exanthematous illnesses and others, as well as vaccines against smallpox, whooping cough, etc. All of these infections and vaccinations determine the formation of antibodies that remain in the organism; hence, man is usually sensitized non-specifically**.** Any antigen penetrating or introduced into the organism, reacts with existing antibodies of other origins there and causes serious manifestations of varying degrees depending on the case, or causes present manifestations to disappear'. Parallergy helps us understand the great variability of clinical cases of each disease, as well as its evolution, from one person to another. Likewise, false-positive or false-negative results of serologic reactions (Wassermann, Widal, etc), based on antigens and antibodies, find their explanation in the phenomenon of parallergy.

The term metallergy (gr., *meta* = change + *allergon*) is used 'to indicate the altered reactions determined by the action of chemical substances introduced to, applied to, or formed by the organism itself, that combine with organic proteins to form haptens (gr., *haptein* = to fasten), also called half-antigens. These haptens react with pre-existing antibodies and cause varied results. Consequently, the negative or beneficial altered reactions determined by medications are also of an allergic nature, or more precisely, metallergy. The negative altered reactions are designated idiosyncrasies or intolerance in medicine'. In certain cases, the specifically sensitized organism responds to later exposures of a different type with specific allergic reactions which reproduces the same clinical symptoms caused by the first agent': contact dermatitis can be triggered again by contact with another chemical agent.

The variations of human idiosyncrasies are related to parallergy and metallergy, which produce distinct clinical and anatomic symptoms in patients with the same disease. 'Disease physiopathology, which constitutes clinical symptomatology, depends exclusively on the manner in which the organism reacts and not on the cause which determined it, nor on the anatomic-pathological lesion; (...). The manner of the organism's reaction results from interaction of the genotype's characters, (...), which are responsible for homeostasis. These characters represent the biological terrain, which varies from individual to individual and even in the same individual, according to age, sex, state of nutrition and time of year'.

Each organism's predisposition to fall ill (idiosyncrasy, biological terrain) is related to the sensitive organ 'which responds to antigen–antibody shock, meaning the organ which manifests the clinical and

anatomic-pathological symptoms of the illness. When an anatomic-pathological examination is possible, it can be verified that it is an organ that has been embryologically altered or retarded in its evolution, that is to say there is a partial constitutional alteration [...]. It is a sensitive organ, (...) the *locus minoris resistentiae* of ancient physicians'.

Maffei explains the observation by Hahnemann that two similar illnesses cannot cohabit the same organism simultaneously, by the theory of RES blockage: 'An individual with an illness can not acquire another concomitantly because the first has already established RES blockage; that is why, in any case, all verified symptoms and signs should be related to the same entity, since no one can have two maladies at the same time. Reciprocally, if the individual has a disease and is able to acquire another at the same time, he will be cured of the first'.

'The same occurs with medications; all drugs act by means of the allergic mechanism. For this reason the effects vary from one individual to another, or even in the same individual, according to the state of R.E.S. blockage. In this way, the same medicine used for the same illness gives good results in one case, yet mediocre or null in another, while a third may be disastrous'. Therefore, pathogenesis of all morbid manifestations is represented in allergy, which allows the understanding of the symptoms and mode of the evolution of illnesses in each individual, as well as the action of different therapeutics.

Analysing pathological alterations of various human diseases (tuberculosis, syphilis, colagenosis, etc), Maffei describes their fundamental and progressive pathological processes according to various reactive phases of the organism by the following histomorphological alterations of the RES: (1) oedema; (2) mucoidosis; (3) fibroid necrosis; (4) fibrosis; (5) elastosis.

The hygiene hypothesis

Physiopathology of chronic allergic processes

Chronic allergic diseases display a bi-phasic inflammatory response, with an immediate and a delayed phase. Immediate inflammatory response occurs in patients with sensitized genetic predisposition (atopy), mediated by IgE antibodies. Upon contact with IgE on the surface of mastocytes and basophils, allergens trigger degranulation, releasing immune mediators, responsible for physiopathological alterations and immediate allergy symptoms. In the second stage, affected organs undergo a chronic inflammatory process with eosinophil, basophil and lymphocyte migration. The pathogenesis of allergic responses is closely related to the preferential activation of specific T *helper* lymphocyte subpopulations, called Th2, (to the detriment of Th1 subpopulations), capable of producing predominantly IL-3, IL-4, IL-5, IL-9 and IL-13 interleukins, which activate mastocytes, basophils and the other inflammatory cells, producing immediate and delayed allergic process responses.[11–13] T *helper* lymphocyte subpopulations are related to the acute cellular immune response, through IL-2, IFN-γ e TNF-β production.

After this introduction of the physiopathology of chronic allergic processes, we will discuss current scientific evidence which indicate triggering chronic allergic diseases (Th2 response pattern) when acute inflammatory diseases (Th1 response pattern) were suppressed or inadequately treated in childhood, or failed to run their natural course.

Hygiene hypothesis

Initially formulated by Strachan[14] in 1989, the hygiene hypothesis aims to explain the empirically observed fact that children who develop acute disease in early life, even if genetically predisposed to develop atopy and other chronic diseases, may remain free from such manifestations. On the other hand, suppression of the natural manifestation of childhood infections through indiscriminate vaccine or antibiotic use can favour the development of atopic and chronic symptoms at a later age. A controversial issue in recent years, the hygiene hypothesis has been the subject of many discussions and reviews[15–28] and a number of experimental trials.

The hygiene hypothesis emphasizes that environmental and socioeconomic factors, associated with improved diagnostic procedures, explain the rise in asthma and other atopic diseases over the last decades in developed societies. The most plausible hypothesis for the fact is that the western life-style (better conditions of hygiene and housing, smaller families, vaccination and the use of antibiotics) is associated with fewer childhood infectious diseases; especially those stimulating Th1 lymphocyte production. This is antagonistic to the differentiation of Th2 lymphocyte subpopulations (the dominant response in the foetus and neonate), and favours an increase of future allergic manifestations. Recent studies provide additional evidence that infections, such as colds, herpes simplex, tuberculosis, hepatitis A and measles, manifesting during childhood, prevent the development of atopic diseases later in life for people with such a genetic predisposition. Exposure to microbial pathogens in childhood, without infections, is sufficient to provide protection against allergic diseases.[29,30] However, the same effect is not observed when children receive vaccines against the same diseases.[31,32]

Despite uncertainty as to which childhood infections play the role of future immunoregulator, the most likely are intracellular and viral microorganisms, which trigger a vigorous immune cellular response (Th1 response). Normal intestinal microflora, affecting systemic immunity through intestinal lymphoid tissue, has shown to have an important role in inhibiting Th2 response to inhaled allergens. This suggests that indiscriminate antibiotic use in paediatrics over the

last decades interferes with this immunological balance.[33] The possible mechanisms involved in infection-induced immunoregulation are related to the two T *helper* lymphocyte subpopulations, Th1 and Th2, which are regulating by reciprocal inhibition. Th1 cells, producers of IFN-γ, IL-2 and TNF-β, cause the cellular immune response and the phagocyte-dependent inflammation, as well as inhibition of the Th2 response. Th2 cells, producers of GM-CSF, IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, cause intense humoral responses (including IgE) and eosinophilia; however they inhibit the function of phagocyte cells. Genetic and environmental factors polarize Th1/Th2 subpopulations.[34–42]

The dominance of Th1 responses is related to the pathogenesis of autoimmune disorders of specific organs, including multiple sclerosis, rheumatoid arthritis, Crohn's disease, sarcoidosis, and some unexplained recurrent abortions. In contrast, Th2 allergic-specific responses are responsible for allergic manifestations. Nevertheless, the dominance of Th2 response also plays an important pathogenic role in progressive systemic sclerosis, in cryptogenic fibrotic alveolitis and favours swifter evolution of AIDS.[43–47]

In spite of the mechanism's complexity, the absence or presence of systemic infections in childhood determines the phenotypic expression of the T-dominant lymphocytes in later life. Repeated infections can select Th1 lymphocyte subpopulations to be detrimental to Th2 subpopulations, (probably via antigens of bacterial DNA and viral RNA) hindering allergic sensitization from manifesting in genetically predisposed children. IL-12 is the chief mediator involved in promoting Th1 lymphocyte differentiation, while IL-4 and IL-10, inhibit the Th1 pattern, predisposing Th2 differentiation. Along with the natural killer (NK) cells, the Th1 lymphocytes produce IFN-γ, creating an environment in which specific antigens induce extensive differentiation of the T memory cells (CD4+), with an increased subsequent production of IFN-γ. Low IFN-γ levels in children indicate a depressed Th1 response and a predominant Th2 response. Thus arises the hypothesis that if IL-12 production does not occur during the first systemic infections of childhood, there will be a prevalence of the Th2 subpopulation in genetically predisposed children. It will then be difficult to restore the Th1/Th2 balance later.[48–50]

Although the critical period for the reversal of Th1/Th2 imbalance is unknown, it is believed that until immune system maturation (5–7 years of age), and especially in the first 2 years of life, systemic infections play a fundamental role in the process. Recent studies, employing the cutaneous sensitization test for common allergens, indicate 5 as the average age for children to be classified as atopic or non-atopic. Even though most studies emphasize the importance of the first years of life for T lymphocyte programming and memory regulation, some research shows Th1/Th2 pattern changes in adult immigrants, who are genetically susceptible to atopy, after increased exposure to infectious diseases.[51,52]

In a review on the effect of different therapeutics on Th2 pattern in allergic diseases, Campbell *et al* (53) compare the effects of drugs with conventional immunotherapy. Some drugs (anti-histamines, corticosteroids, beta-adrenergic antagonists, sodium cromoglycate, etc) did not promote satisfactory alteration in the atopic immunological response pattern (↑IgE allergen-specific; ↓IgG allergen-specific, ↓IgG_4; ↑PGE_2, ↓AMPc; ↑IL-4 allergen-specific, ↑IL-5, ↑IL-13; ↓IFN-γ and ↓TGF-β; ↑proliferation of T allergen-specific cells) and prolonged use led to impairment in some cases. However conventional immunotherapy reversed atopic predominance after several months and maintained the profile for several years: ↓immediate cutaneous reaction; ↓IgE allergen-specific (Th2 Th1); ↑IgG allergen-specific, ↑IgG_4; ↓IL-4 allergen-specific; ↓IL-5; ↑IFN-γ; ↑TGF-β; ↓proliferation of T allergen-specific cells. Other reviews (54) confirmed these findings.

Thus, a therapy that stimulates the organism's healing response through the principal of identity (*aequalia aequalibus curentur*), approximating the mechanism of action of the homeopathic principle of similitude (*similia similibus curentur*), works at deeper levels than therapeutics using the principle of opposites (*contraria contrarius curentur*).

Using the hygiene hypothesis (see Table 1) for other chronic manifestations, Rouse[66] discusses a number of possibilities regarding the variation in individuals' susceptibility to primary infection by herpes simplex virus (HSV) and why some individuals suffer from recurrent lesions due to viral reactivation. He raises the hypothesis that several aspects of inborn immunity, conditioned by microbial exposure in early life, can affect susceptibility to HSV infection, the nature of the initial immune response and the efficacy of subsequent memory reactivation. In a similar manner, it was suspected that the increase in appendicitis in developed countries, in contrast to that in Third World countries, can be related to improved hygiene, which limits the exposure to and development of enteric infections and benign viruses, leading to future appendicitis.[67,68]

Smith *et al* (69) based their study on findings showing the incidence of acute lymphoblastic leukaemia (ALL) in children. It showed higher rates of temporal and geographic variation in developed countries in the first-half of the 20 century and lower rates for developing countries. They sought to evaluate the relationship between ALL in infancy and hygiene conditions, an aspect of socioeconomic development that affects exposure rate to infectious agents. The Hepatitis A (HAV) infection pattern (oral–faecal transmission) was used as an index of hygiene. An inverse relationship was observed between the prevalence of HAV infections and leukaemia rates in infancy. Further there were decreases in the HAV infection rates in the United States and Japan, which

Table 1 Clinical studies of the hygiene hypothesis

Authors	*Study model*	*Objective*	*Results—conclusions*
Farooqi and Hopkin[55]	Retrospective epidemiological study	Relationship between childhood infections, immunizations and subsequent atopic diseases in 1934 people	Three indicators: maternal atopy, immunization for *B. pertussis* and antibiotic treatment in the first 2 years of life
Illi *et al*[56]	Longitudinal cohort study	Relationship between infections in early infancy and subsequent development of asthma or asthmatic symptoms in 1314 children	Repeated viral infections in childhood (excluding the lower respiratory tract) could reduce the future risk of asthma development
Droste *et al*[57]	Longitudinal cohort study	Relationship between antibiotic use in the first year of life and subsequent development of asthma and allergic disorders in 1206 children.	Early use of antibiotics in infancy was associated to an increased risk of developing asthma and allergic disorders in predisposed children
Matricardi *et al*[58]	Controlled study	Relationship between exposure to alimentary and orofaecal pathogens, compared to airway viruses, with atopy and respiratory allergies	Using serology tests, the authors concluded that respiratory allergies are less frequent in people exposed to orofaecal and foodborne pathogens
Brooks and Lemanske[60]	Clinical trial	Association between rise in endotoxins in domestic environments and prevalent decrease of allergen sensitization in 61 children	Authors concluded that endotoxin exposure during infancy is associated with a reduced prevalence of allergenic sensitization and a rise in the proportion of Th1 subpopulations
Kalliomaki[61]	Placebo-controlled trial	Effect of *Lactobacillus GG* on athopic diseases by prenatal administration to atopic pregnant women	*Lactobacillus GG* was effective in atopic disease prevention when administered to high-risk children at an early age. Other trials showed similar results.[62,63]
McKinney *et al*[64]	Controlled study	Evaluate the patterns of social mixing and infections in the first year of life with the risk of developing autoimmune diabetes in genetically predisposed childhood	Social mixing provided protection against developing childhood diabetes because the exposure to infections can play a role in the development of protective immune mechanisms
Gibbon *et al*.[65]	Controlled study	Relationship between exposure to infections during infancy and development of type 1 *D. mellitus*	The authors concluded that decreased exposure to common infections during infancy could be linked to subsequent development of type 1 *D. mellitus*

were seemingly preceded by increased rates of infant leukaemia. Attempting to explain this, the authors describe a model based on a supposed leukaemia-inducing agent related to the changes in the HAV infection rate. This model supports the hypothesis that lessened exposure to a leukaemia-inducing agent in childhood, associated with improved hygienic conditions, results in higher ALL rates in children. On the other hand, we cannot discard the hygiene hypothesis as a model to explain the fact if we consider the Th1 response as the most effective in viral infections (viral leukaemia-inducing agent) and the Th2 response as 'the cause of chronic processes in general.'

Discussion

This review's central theme is to correlate inhibition of natural manifestation of acute diseases in childhood with the occurrence of later chronic diseases. The observations of homeopathic physicians find a scientific basis in other areas of modern medical knowledge. According to Hahnemann, 'every clinical manifestation originates from the abnormal reaction of the organic vitality to a morbific agent'. He states that human diseases can be divided into two categories: 'acute diseases', strong vital reaction in a short period of time, show a swift and satisfactory response of the organism, and 'chronic diseases', which develop for longer periods. The organism's predisposition to developing either type of disease is based on the 'reaction capacity of the organic vital energy'. Acute diseases are triggered by momentary harmful, external stimuli or by acute and contagious miasms, generally returning to their state of basal equilibrium. Chronic diseases, on the other hand, are artificially triggered by pernicious medicinal treatment or, naturally, by chronic miasms (*psora, sycosis* and *syphilis*), causing greater derangement of the reactive vital energy, and a difficulty into returning to the initial order.

Hahnemann's views are close to Maffei's; we can correlate the Hahnemannian concepts of 'acute diseases' to the phenomena of 'immunity' and 'chronic disease' to the phenomenon of 'allergy'. Following an

antigenic attack (acute miasm, for example), when the reactive process of 'immunity' (effective humoral reaction to antigens, which allows unstable health to regain balance) is lacking, the result is 'allergy'. Allergy, or the RES's altered reaction of tissue to antigens, covers most symptomatic manifestations of chronic diseases.

Box 1 Disease, immunity and allergy

- disease ⇔ altered reaction of vital energy (RES) to aggressive agents(antigens)
- immunity (positive anergy) ⇔ normal, balanced vital reaction ⇔ acute diseases
- allergy ⇔ abnormal unbalanced vital reaction ⇔ chronic diseases

Maffei divides allergy into 'hyperergy' (swift, effective, intense reaction) and 'hypoergy' (weak, in effective reaction) and 'negative anergy' (lack of reaction). This corresponds to *psora, sycosis* and *syphilis,* respectively. Bear in mind that an acute hypergic manifestation is curbed by immunity, and can disappear from the organism ('positive anergy') without becoming a chronic disease.

'Metallergy' corresponds to the organism's modified reaction to medicines, which is similar to the 'artificial chronic diseases' cited by Hahnemann. The symptoms of morbid disorders occurring after vaccination (called 'vaccinosis' by Burnett), Maffei classifies as 'parallergy' (result of non-specific antigen-antibody shock):

Box 2 Mattei's classification of defensive reactions

- hyperergy (swift, intense, specific reaction) ⇔ *psora* (skin pruritus)
- hypoergy (weak, slow, specific reaction) ⇔ *sycosis* (tissular proliferation)
- negative anergy (lack of reaction) ⇔ *syphilis* (tissular destruction)
- metallergy (medicinal reaction) ⇔ chronic artificial disease
- parallergy (vaccinal non-specific reaction) ⇔ vaccinosis

The French homeopaths' miasmatic conception, resembling those of Hahnemann and Maffei, defines disease as the organism's modified reaction (vital energy) to aggression. We can relate 'allergies' and 'chronic miasms' to 'constitutional types' and modes of RES 'reaction' and 'elimination' of aggressive agents.

Box 3 Bernard's constitutions and their relationships to chronic miasms

- sulphuric constitution ⇔ swift, intense, effective RES reaction ⇔ centrifugal toxin elimination ⇔ hyperergy ⇔ *psora*
- carbonic constitution ⇔ slow and torpid R.E.S. reaction ⇔ centripetal toxin elimination ⇔ hypoergy ⇔ *sycosis*
- phosphoric and fluoric constitution ⇔ ineffective and chaotic reaction ⇔ no toxin elimination ⇔ negative anergy ⇔ *syphilis*

Maffei explains the observation that acute infectious disease manifestation can promote the prevention or cure of chronic diseases through 'shock organ displacement' by 'blocking the RES.' In a similar manner, he attributes to vaccines (parallergy) and some medicine (metallergy) the characteristic of promoting (and curing) serious manifestations in individuals who are previously sensitized or genetically predisposed.

The homeopathic clinical observations that suppression of natural manifestation of acute diseases can cause future chronic diseases led me to the 'hygiene hypothesis'. This theory explains the rise in chronic and allergic diseases in western societies in which lifestyles are characterized by excess of hygiene, social isolation, antibiotic therapy and excessive vaccinations leading to an imbalance between Th1 and Th2 lymphocyte responses. Children's contact with a number of pathogens are reduced; this impedes acute infectious disease manifestation in early childhood, inhibiting the activation of Th1 lymphocyte subpopulations and favouring activation of Th2 subpopulations, responsible for allergic and chronic manifestations.

Box 4. Lymphocyte subpopulations and their relationship to disease

- Th1 lymphocytic response ⇔ immunity ⇔ acute diseases.
- Th2 lymphocytic response ⇔ allergy ⇔ chronic diseases.
- Th1/Th2 balance ⇔ RES blockage ⇔ acute/chronic disease.

This hypothesis explains the increase in allergic diseases in developed countries, as well as the greater incidence of other chronic diseases (type 1 diabetes, appendicitis, herpes simplex, ALL, etc). Moreover, the prevalence of the Th2 response plays a pathogenic role in progressive systemic sclerosis, cryptogenic fibrotic alveolitis and favours faster evolution of AIDS. On the other hand, autoimmune diseases due to overproduction of Th1 cytokines and increased monocyte production of IL-12, protect the organism against allergic disease. This shows a reciprocal antagonism between the two abnormal modes of reaction of the RES to external stimuli.

Box 5 Summary of theories of pathogenesis of chronic disease

- Hahnemann—'chronic artificial disease'
- Henri Bernard—'chronic reticuloendotheliosis' or 'sycosis'
- Maffei—'oedema, mucoidosis, fibrinoid necrosis, fibrosis, and elastosis'
- Hygiene Hypotheses—'Th2 lymphocytic response'

I believe that homeopathic treatment, like conventional immunotherapy, acts on Th1/Th2 imbalance, regulating the exacerbated Th2 response of allergic and chronic diseases. In a homeopathic clinical trial (individualized, randomized, and placebo-controlled) for perennial allergic rhinitis that we are developing,

we propose to evaluate the immunological response pattern to homeopathic treatment by measuring immunological markers during treatment.

In developing the isotherapy clinical trials of Reilly *et al*,[71–74] we suggest longer periods (6–12 months) of patient treatment and follow-up. In addition, measurement of immunological markers should be carried out before, during and after therapy.

Conclusion

I have sought scientific evidence to endorse the belief that inhibition of acute disease manifestation in childhood can predispose to future of chronic diseases. This clinical observation, empirically cited over the centuries, has limited acceptance by researchers who seek to prove homeopathic paradigms according to modern and scientific reasoning.[75–76] However, sizeable research projects examined, focusing on experimental pathology and the hygiene hypothesis. Many homeopathic concepts, founded on observation of clinical symptoms, will be vindicated by the study of allergy. The study of the phenomena of health and disease through the prism of integrative physiopathology (neuro-immuno-endocrin-metabolic), the holistic view of the human being, as described in the homeopathic model with its phenomenological focus, can be understood according to the parameters of modern diagnostic evaluation.

Regarding the controversial subject of vaccines, homeopaths cannot deny the immense legacy they have brought to collective health, eradicating a series of epidemics which continue to ravage humanity in underdeveloped regions, that lack basic health care. On the other hand, non-homeopathic physicians must be aware that the goal of collective immunity to acute diseases can lead to chronic diseases in a predisposed portion of the population, with future consequences that are currently difficult to measure. The intensity of the accommodation phenomenon (acute diseases *vs* chronic diseases) and seriousness of chronic diseases that have become more prevalent, resembling veritable 'chronic epidemics' should be investigated in future population studies. This will broaden the debate over the indiscriminate use of vaccines, corticosteroids, non-steroidal anti-inflammatories, hormone replacement therapy, etc.

To scientifically establish homeopathy as therapy in the treatment of human illnesses, research should be developed to measure the range and amplitude of its prophylactic and curative therapeutic practices, compared to conventional therapy.

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