English translation of the german original

16th Part — Allergology

Allergens, microbial and environmental factors as the causative triad in the pathogenesis of atopic diseases

Since the current statistics in the Federal Republic of Germany show that there are over 25 million allergy sufferers while, at the same time, press releases report on new environmental scandals almost every week, then it is perhaps legitimate to ask whether there is a connection between the terms "allergy explosion" and "environmental pollution". This development was practically unknown until the second half of this century, but in the last 20 - 30 years in particular, parallel to the increasing environmental pollution, we have noticed a rapid spread of allergies, especially in urban areas.

Summary

A causal relationship between increasing environmental pollution and the rapid spread of allergies has been increasingly discussed in recent years. The total environmental load caused by exogenous and endogenous noxious agents is evident in animal experiments and in humans, primarily through immunotoxic, sensitizing and neurotoxic effects.

In addition to known conditioning factors of allergic reactions (sensitizing potency of the allergen, intermittent exposure to different allergen concentrations, presence of microbial bodies and potentiating phenols), an increasingly important adjuvant role for the induction of allergy is attributed to certain environmental pollutants.

Our own experience in treating over 15,000 atopic dermatitis patients shows that, in addition to allergic reactions, pseudo-allergic reactions caused by toxic irritant environmental factors (formaldehyde, exhaust fumes, wood preservatives, microbial toxins, food rich in additives, nicotine, alcohol, pesticides, solvents, amalgam, heavy metals and others) are increasingly coming to the foreground as the cause of the complex symptoms. Early elimination of harmful substances of an exogenous and endogenous nature before and during pregnancy as well as in the first years of life can significantly reduce the incidence of atopic diseases.

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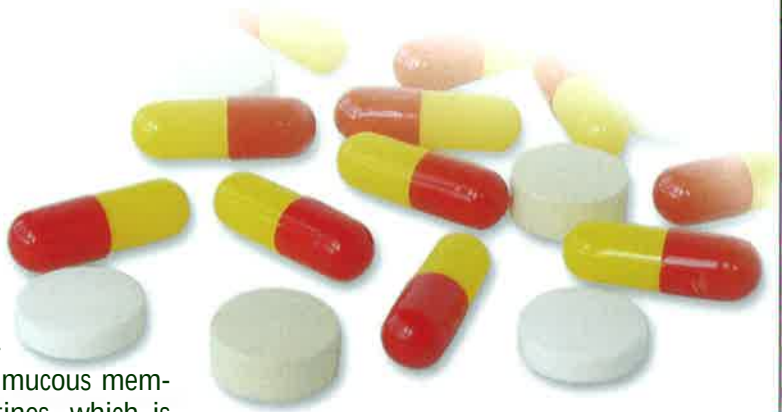
Total exposure to negative environmental factors

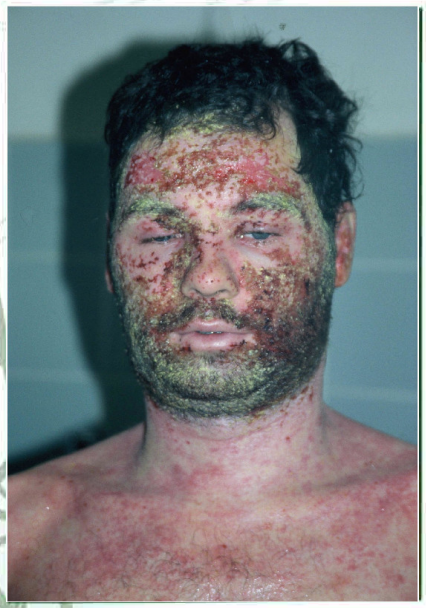
There are currently estimated to be over 7 million chemical compounds with an annual growth rate of more than 250,000 new substances. We come daily in contact with over 50,000 of these. E.g. irritant exhaust gases from vehicles and industrial plants (SO_2, NO_2, CO_2), from heating and combustion plants, excess ozone, industrial dust or tobacco smoke, as well as soil and water pollution through pesticides, fertilizers, insecticides, heavy metals and chemical and radioactive residues of all kinds. In the household or at the workplace we are also not spared the negative effects of various pollutants such as asbestos, formaldehyde, wood preservatives, adhesives, solvents of all kinds, oils and petrol, resins, detergents, and heavy metals.

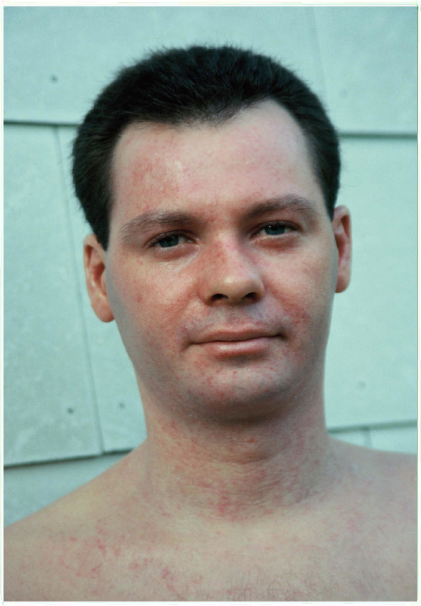
In addition, we experience the side effects of a whole range of additives through the daily intake of semi-prepared food. These includes the preservatives, colourings, binding agents, gelling agents, emulsifiers and flavour enhancers labelled "E" , which "give" our food its long shelf life, appetising appearance and desired taste. Active ingredients and additives from cosmetics, drugs and pharmaceuticals also frequently contribute to various intolerance reactions, in addition to dyes and synthetic fibers from the textile industry. Allergic and environmentally sensitive patients also react sensitively to the negative effects of electromagnetic fields from a wide range of electrical appliances, from screen computers and televisions to stereo systems, aerials and high-voltage power lines, as well as radioactive radiation from environmental residues or medical irradiation equipment. If the influence of daily psycho-social stress (distress) is added to all these factors, an initial picture of the physical stress caused by exogenous environmental noxae emerges. However, the function of various organ systems can also be additionally impaired by the presence of chronic infections caused by bacteria, viruses and yeasts that colonize the skin and the mucous membranes of the respiratory tract and, above all, the gastrointestinal tract. Various gene polymorphisms of the 1st or 2nd detox phases enzymes (GST, NAT2, UDP-glucuronyltransferase, sulphotransferase, etc.) play a significant



role. Their metabolic and degradation products (endo-, exo- and mycotoxins, indole, skatole, phenol, biogenic amines and others) together with the release of toxic heavy metal residues from pessaries, amalgam fillings, crowns and dental bridges or ionomer substances from various implants (plastics, silicone, acrylates, dental cement) form a second group of endogenous stress factors, which also contribute to a cumulative toxic increase in the overall burden.

Years ago, American authors introduced the term total environmental load as a measure of the total exposure to environmental stressors [1]. The contact with the above-mentioned foreign substances and chemicals occurs primarily in the respiratory tract via the air we breathe, in the gastrointestinal tract via food and drinking water and via the skin and causes very different effects. Most toxins attack the metabolic processes and cell structures of the immune system and/or the central nervous system through the skin and mucous membranes. As a direct consequence, immunotoxic or mitogenic effects on the blood cell subpopulations are registered [2, 3] as well as a decrease in secretory immunoglobulins [4,5], usually associated with an increased susceptibility to infections of the skin, mucous membranes and intestines, which is particularly pronounced in allergy sufferers [6]. The neurotoxic effects of environmental pollutants are diverse and can manifest themselves in the form of headaches, dizziness, difficulty concentrating, tremors, lack of motivation, sleep disorders and cardiac arrhythmias, as well as paralysis and depressive states [7-10]. The impaired release of catecholamines in environmentally sensitive hyperkinetic patients (dopamine) and atopics (noradrenaline) has also been reported [11, 12]. Some of the pollutants are also stored in fatty tissue, connective tissue, bones and the nervous system and are occasionally mobilized again with negative effects for the affected person. Analytical tissue examinations can clearly document this.





Clearly visible success in the therapy of a neurodermatitis patient

Due to the increasing frequency of cases, new medical terms have emerged in recent years, such as multiple chemical sensitivity or sick building syndrome, with extremely broad abnormalities in various organ systems and symptoms. Some of those affected believe that they are suffering from an allergy to environmental chemicals, although this allergy cannot be detected using conventional immunological tests. On the other hand, allergists have found that most diagnosed allergy sufferers with asthma, atopic dermatitis, allergic rhinitis or urticaria are also environmentally sensitive patients with an increased hypersensitivity to the smallest concentrations of various environmental chemicals and biogenic toxins. Their symptoms are always due to a mixture of allergic and pseudo-allergic reactions. People are already talking about allergotoxicology as a current interdisciplinary field to which allergy sufferers and environmentally sensitive patients are assigned.

Provocative factors of allergic reactions

A complex interplay of different blood and tissue cells such as macrophages, lymphocytes, eosinophils, basophils, PMNs and mast cells mediated by their inflammatory substances (cytokines) is of decisive importance in the induction of a normal immune response or allergic reaction and the resulting inflammatory components. According to Coombs and Gell, a distinction is made between immediate and delayed allergic reactions of types I to IV.

The immune system is always involved. In addition to a hereditary predisposition to 'atopy' manifestation, which is strongest when both parents are atopic (prevalence of atopy of 60 - 80 % in the filial generation), various factors play an important role in the development of an allergy. These include:

1. The sensitising potency of the allergen

It is known, for example, that early weaning and the administration of formula feeds based on strong allergens such as cow's milk, soy or foods containing egg and yeast can lead to allergy induction in infants [13]. The chemical composition of the so-called haptens is decisive for the sensitisation potency. Repeated intermittent exposure to different allergen concentrations is also a known prerequisite for the induction of an allergy.

2. The microbies [14]

These and various irritants such as phenols (Freund's adjuvant) also influence the induction of an IgE response and allergy in animal experiments. Similar effects must be expected, for example, in infants who were infected early on by facultative or obligate pathogenic germs from the maternal birth canal or the hospital (Staph. aureus, haemolysing E. coli, Proteus, Klebsiella, Pseudomonas, Candida albicans, etc.), which can lead to contamination of the intestine with abnormal flora.

Similar microbial conditions with the production of large quantities of sensitising degradation products (including phenol) can also develop later as a result of intestinal flora-decimating antibiotic treatments or under the influence of immunosuppressive radiotherapy, cytostatic or cortisone therapies. Such dysbiotic conditions of the intestine have become a characteristic of allergic diseases [15].

3. Various environmental pollutants are thought to play an adjuvant role in the induction of allergy. Several mechanisms come into question here:

- Damage of the skin and mucosal barriers caused by chemical, physical or microbial influences via direct damage to the cell membranes and release of inflammatory mediators such as histamine, prostaglandins and leukotrienes, e.g. after exposure to pesticides [16, 17], alcohol and microbial toxins. The increased permeability of the mucosal barrier leads to increased allergen uptake and sensitisation [18].
- Increased IgE production with the onset of allergic symptoms has been described after exposure to irritant and Diesel exhaust gases [19], cigarette smoke [20, 21], mercury compounds [22] and platinum salts [23]. The increased pollution can exert its effect at different cellular levels, depending on their absorption and stimulus potential.
- Induction of IgE synthesis after binding of pollutants to serum proteins (e.g. formaldehyde and formaldehyde derivatives) [24] with formation of novel antigen structures.
- Conformational change of the cell surface after contact with heavy metals with sensitising effect for antigen-specific T lymphocytes with subsequent induction of proliferation and differentiation (contact allergies) [25, 26]
- Changes in the intermediate metabolism by influencing the structure and biological activity of various enzyme systems, RNA, DNA and protein syntheses (Hg^{2+}/SH-proteins; DNase, ATPase, methyl Hg/oxidative phosphorylation; alcohol, nicotine, MAO, DAO) [27-31].

As a rule, the symptoms of allergic and/or environmentally sensitive patients are the result of interactions with exogenous pollutants and/or endogenous noxious substances. This also explains the polymorbid clinical conditions that these patients exhibit. The importance of preventive medical measures with avoidance of allergens or environmental toxins and an appropriate health attitude, including in the psycho-social area, is evident.

Allergotoxic factors in atopic dermatitis (AD)

It is not only our own experience in the treatment of over 15,000 neurodermatitis patients that shows that, in addition to allergic mechanisms, pseudoallergic reactions caused by toxic irritant environmental factors (formaldehyde, exhaust fumes, food rich in additives, nicotine, wood preservatives, pesticides, heavy metals) are increasingly coming to the foreground as the cause of the complex symptoms; the intrauterine and postnatal influences of such factors have also been reported [32, 33].

Of particular interest in neurodermatitis patients is the occurrence of allergic and pseudo-allergic reactions to foods and additives, which we have investigated in controlled studies before and after test meals [18].

In addition to clear deviations in the serum values of circulating immune complexes and specific IgE and IgG4 antibodies against food, investigations of serum histamine levels in atopic dermatitis patients before and 1/2 h after test meals show a highly significant increase in the mediator after food intake. However, as high histamine levels are very often also present in the fasting serum of atopic dermatitis patients, we investigated the degradation pathways of this biogenic amine. Diamine oxidase (DAO) is the key degradative enzyme for histamine, but monoamine oxidase (MAO) is also involved in the degradation pathway. In a study on MAO and DAO activity in the platelet-rich plasma of atopic dermatitis patients and control subjects, we were able to show that the activities of both MAO and DAO were significantly lower in atopic dermatitis patients compared to control subjects. At the same time, we found a significant increase in histamine levels in the same atopic patients. It is known that high concentrations of biogenic amines such as putrescine, octopamine, histamine etc. inhibit these degradative enzymes.

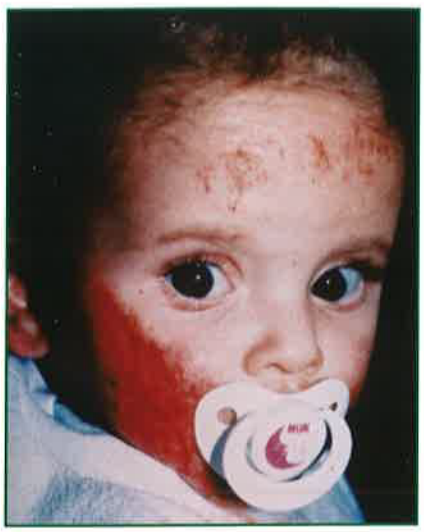
Other inhibiting factors are additives from food, heavy metals, alcohol and nicotine, whereby alcohol also leads to increased absorption of biogenic amines from the gastrointestinal tract. Some medications, such as certain antidepressants, also act as MAO-blockers. The cofactors for MAO (iron and FAD) are reduced in AD patients, while the cofactors for DAO (copper and pyridoxal phosphate) are almost normal, which suggests an excess of the above-mentioned enzyme inhibitors [31]. These findings explain the pseudoallergic, i.e. non-immunological reactions to certain foods, such as frozen fish, in which histamine levels are up to 10 times higher than in fresh fish. High histamine concentrations are also found in various types of cheese, sauerkraut, pickled cucumbers and canned tomatoes. Pseudoallergic reactions also occur against other biogenic amines such as tyramine, phenylethylamine and putrescine due to a deficiency or inhibition of the degrading enzymes MAO and DAO.

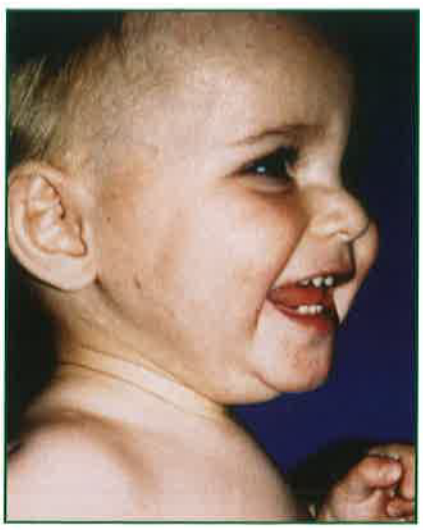
We find high concentrations of the biogenic amine tyramine in mushrooms, grapes, sausage, red wine, sparkling wine and certain types of cheese, for example.

The generally increased intestinal permeability in atopic patients and significantly increased antigen absorption, which in turn can lead to higher circulating immunocomplex levels, activation of the complement system and the coagulation cascade and degranulation of mast cells and basophils [18], also prove to be a significant pathological aspect.

However, a direct correlation between the higher intestinal permeability values on the one hand and the serum histamine values or the presence of IgE-containing CICs on the other could not be established. The cause of the increased intestinal permeability lies in a clear intestinal dysbiosis, which is present in almost all of our atopic dermatitis patients and is associated with an excess of facultative pathogenic bacteria and fungi and a reduction in healthy lactic acid-producing bacteria. In a summarising study with 110 atopic dermatitis patients [15], we were able to prove that in almost 50 % of the cases examined there were significantly reduced levels of lactobacilli and bifidobacteria and a massive increase in facultative pathogenic germs such as haemolytic E. coli, Klebsiella, Proteus, Clostridia and yeast fungi such as Candida and Geotrichum. In the same study, the lactose malabsorption test showed significantly lower levels of galactose in the blood and urine of atopic dermatitis patients compared to healthy controls. It is well known that lactose malabsorption is caused by a deficit in lactase activity.

This is the explanation for the widespread intolerance reaction of atopic dermatitis patients to sugar and sugar products. This is a type of pseudo-allergic reaction caused by a secondary dissaccharidase deficiency, which can manifest itself in diarrhoea, intestinal colic, migraines, reddening of the skin and oedema. The undigested and unsplit sugars are used in the intestine for the proliferation of pathogenic bacteria and especially fungi.





This little patient could also be helped.

Amongst the the most important inhibitors of lactase activity are Candida albicans and haemolytic E. coli [34, 35].

Through fermentative processes, various intestinal yeasts and bacteria convert the unsplit carbohydrates into organic alcohols [36] and short-chain fatty acids with a narcotic effect [37, 38], which explains the pronounced postprandial fatigue and alcohol intolerance of patients and also leads to an increase in intestinal permeability. The yeast fungi produce phospholipase A2, which breaks down membrane phospholipids, which are converted via arachidonic acid to prostaglandins and leukotrienes with considerable inflammatory potential. Toxic meat degradation products (indole, skatole, phenols, biogenic amines), produced by a putrefactive flora (Clostridia, Bacteroides sp., pathogenic Enterobacteriaceae) also contribute to irritation of the skin, the mucous membranes and the nervous system and act as adjuvant factors (phenols) in the induction of IgE synthesis (see Freund's adjuvant).

Impaired energy metabolism and regulatory factors

Other side effects of the incorrect intestinal colonization were discussed in detail in an earlier study [15]. The reduced carbohydrate absorption caused by inhibition of the dissaccharidases together with the impairment of the intermediary metabolism by environmental pollutants of various kinds (PCP, pesticides, exhaust fumes, heavy metals, polychlorinated biphenyls, microbial toxins and others) causes a markedly reduced production of energy-rich substances (ATP) in allergy sufferers. This is also one of the most important causes of the low levels of cyclic nucleotides (cAMP) with a regulatory/control function in the release of inflammatory mediators. The cAMP levels are further reduced by the simultaneous blockade of the beta-adrenoceptors [39, 40] and the increased activity of the degrading enzyme phosphodiesterase [41].

Heavy metal exposure in atopic dermatitis

The immunotoxic and allergotoxic relevance of heavy metal contamination (cadmium, lead, platinum, copper) has been increasingly reported in recent years [2, 42-45].

Mercury has been given a special role, especially due to the heated discussion on the subject of 'amalgam'. It is important to distinguish between the allergic potential of mercury (up to 17% allergy incidence with a positive epicutaneous test) and its chronic toxic potential, which can lead to an accelerated summation effect with other noxious substances, particularly in allergy sufferers. Several mechanisms of attack are referred to here, e.g.:

- Binding to serum and cell proteins (albumin, coenzyme A, SH-proteins) with effect on the intermediate metabolism [27];
- Increase in the cellular mitotic rate in lymphocyte populations [46];
- Induction of IgE synthesis with increase in allergen-specific IgE response in rats [22];
- Decrease in T lymphocytes, T-helper cells and NK cells after mercury mobilisation from amalgam fillings [47, 48];
- Promotion of inflammatory reactions through activation of corresponding enzyme systems (e.g. collagenases [49]).
- Of particular importance for patients is the conversion of the ionised Hg^{2+}-form by methylation into a much more toxic, lipid-soluble organic compound (methylmercury) [27]. Oral and intestinal bacteria (Streptococci, Clostridia) [50] and in particular yeast fungi (Candida albicans) [51] also play a decisive role here and provide one explanation for the differences in symptoms from one amalgam carrier to another.

Even if the clinical relevance of these results for the pathogenesis of neurodermatitis is still being discussed, the most important sources of mercury always remain the same, in principle: as an additive in various medications (in ointments, drops, vaccinations, etc.), fish-rich food, offal (from 0.3 to 2.3 µg/day) and especially amalgam fillings (3 to 17 µg mercury vapor/day) [27]. Mercury has a pronounced affinity for organs such as the epithelium of the gastrointestinal tract and the skin, for hair, thyroid, liver, pancreas, kidneys and for the brain, especially in the grey matter, as well as in core areas of the brain stem and in the cerebral cortex [52-54]. Magnetic resonance imaging examinations of the head are no longer feasible if patients wear heavy metal alloys in their mouths [55]. Our own investigations in neurodermatitis and psoriasis patients using the so-called chewing gum test show a considerable release of mercury, which correlates directly with the number of fillings [56]. This phenomenon is not only important for patients, but also for pregnant women and mothers, because according to recent findings, the release of mercury leads to transplacental exposure of the foetus [33, 57] as well as the infants through breast milk [58]. Mobilisation from the fillings is particularly high when consuming hot drinks (coffee, tea), fruit juices, fresh fruit or chewing gum. The allergotoxic effect of mercury is often potentiated by the synergistic effect of other environmental pollutants (pesticides, dioxins, furans and others) from breast milk [32].

In our experience with over 15,000 allergy sufferers, two facts are certain:

a) Drilling work in the amalgam fillings of allergy sufferers without appropriate protective measures (rubber dam, antioxidants) usually leads to a rapid worsening of symptoms.

b) Therapy-resistant, recurrent problem areas in the head, neck and facial skin as well as chronic hay fever and throat symptoms remain permanently absent after removal of the amalgam fillings followed by appropriate elimination measures [59]. Recently (March 2006), the EU Parliament came out strongly against the continued use of amalgam in dentistry and is also in favour of a severe restriction on the use of mercury in dentistry and other areas.

Prevention and therapy

Important preventive measures for allergy sufferers are already in place for pregnant women, where avoiding strong allergens in food, alcohol, nicotine and exogenous pollutants can lead to a reduction in the newborn's risk of atopy [13]. The cleaning-up of endogenous stress factors such as infections of all kinds, of the skin, mucous membranes, the birth canal and the intestines is also justified. In the treatment of neurodermatitis, it has been shown that a low-allergen diet, which is offered in a rotation system, together with the remediation of microbial foci, pollutant-removing, immunomodulating and psychological care interventions can make an important contribution to long-term and sometimes durable freedom from symptoms [60, 61].

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