HOW TO DEAL WITH ENVIRONMENTAL PATIENTS

Kurt E. Müller discusses therapeutic strategies

Introduction

A thorough understanding of the pathomechanisms of disease is a prerequisite for successful causal therapy. If this understanding is lacking, treatment strategies will be directed only toward alleviating the symptoms of a disease, not toward eliminating its underlying cause. Prevention, therefore, – the true goal of medical intervention – will not be achieved. This reality applies even more so for children than for adults; the physical and psychological constitution of children develops and changes so rapidly that the pathogenic effects of various factors, including environmental factors, become extremely difficult to clarify. Furthermore, while an evidence-based approach to establishing diagnostic and therapeutic concepts should obviously be followed, one should be aware that evidence itself is a fragile instrument: inappropriate experimental design, manipulation of data, or biased reporting of results can all affect the „evidence“ just as much as how the study itself was financed. Further complicating the situation is the fact that neither evidence nor statistical significance is completely free of human error.

Variability of risk and efficacy of therapy

The risk of a particular chemical affecting human health is generally determined toxicologically by analyzing dose-response relationships following acute or subacute exposure. Long-term effects are then generally extrapolated from these data. However, in establishing such risks for adults, not to mention children, critical factors such as genetic polymorphisms of metabolizing enzymes, the synergistic risk of complex chemical mixtures, and alterations in neuro-immuno-endocrine communication and subsequent functions resulting from chronic low-dose exposure, are rarely taken into consideration. These factors play a significant role in determining not only individual risk but also the form and extent of therapy. In respect to children, these factors unfortunately are never considered. Yet, the situation of children is complicated by the following aspects:

- children have a more rapid metabolism
- children have a higher respiratory volume per kg of body weight
- children have a two-and-a-half times greater skin surface area compared to their weight
- children have approximately double as much water per cell volume
- children absorb toxins more efficiently via the GI tract
- children’s detoxification enzymes are less efficient
- liver and kidney detoxification systems function less well
- their nerve cells are less well protected
- their immune system is still developing
- the development of their central nervous system is completed only between their 16^{th} and 18^{th} year of life.

It should, therefore, come as no surprise that risk estimates for even relatively well-studied chemicals like drugs and medications - in respect to optimal doses for children - are yet to be established.

Immunological effects of chronic exposure to phthalates

Although evidence for detrimental effects of phthalates on the endocrine system of children is accumulating, such evidence so far does not provide the basis for a therapeutic consensus. On the other hand, the various well-studied immunological effects have led to a variety of therapeutic proposals.

Induction of specific IgE antibodies

While the production of specific IgE antibodies to phthalates is associated with practically all symptoms characteristic of atopic disease, respiratory tract reactions are seen most commonly. Therefore, therapies relevant for atopic diseases, in particular allergic bronchial asthma, are applicable.

Induction of interleukin-10 (IL-10)

The increased expression of IL-10 by lymphocytes from patients exposed to phthalates is often correlated with an increased prevalence of atopic disease. Complicating this picture is the increased risk of developing a chronic infection with intracellular microorganisms such as Epstein Barr Virus (EBV), cytomegalovirus (CMV), rotavirus, mycoplasms, or chlamydia. Besides symptoms typical of atopic disease, unspecific symptoms such as chronic fatigue, lack of concentration, or general malaise often predominate. Therapeutic approaches, therefore, have to deal with the infections as well as the atopic symptoms.

Induction of interferon gamma (IFNγ)

Expression of IFNγ alone can induce increased sensitivity of a myriad of cell systems leading not to allergic but inflammatory intolerance reactions not associated with clonal expansion of T lymphocytes. This in turn substantially increases the risk of developing a strong sensibilization to chemically-unrelated toxins. IFNγ also favors the development of autoimmunity. While the synthesis of IFNγ can be suppressed by corticoids, its function is not affected. On the other hand, autoimmune reactions can be induced by a variety of substances (cyclophosphamides, azathioprine, methotrexate, cyclosporin, rapamycin, tacrolimus), all of which have to be considered in the differential diagnosis and treatment.

Induction of interleukin-2 (IL-2)

The increased release of IL-2 results from clonal expansion of previously sensitized T lymphocytes and can be further accentuated by an increase in IFNγ. This process corresponds to the classical type IV allergy in which epidermal uptake of antigen is associated with eczema. By contrast, systemic, inhalative or ingestive uptake can lead to a more complex clinical picture with multiple organ and organ system involvement, including the central nervous system (CNS). This would explain the depression often seen in such patients. In keeping with this, data published by the American Institute Express Scripts reporting a doubling of prescriptions for antidepressants for girls under the age of 5 and an increase in 64% for boys of the same age from 1998 to 2002, would appear to be quite relevant, if we follow the interesting results of Maes, who could show the interaction of inflammation, sensitization and depression.

While corticoids are useful in suppressing clonal expansion of sensitized lymphocytes, caution is warranted, as they have been reported to induce psychoses, at least in adult patients with CNS involvement. Furthermore, there is so far no treatment available for the cell-mediated responses to phthalates analogous to chelation for treating cell-mediated responses to heavy metals.

The role of nutrition and food supplements

The extent to which free radicals and nitric oxides are produced determines the extent of damage caused by chronic exposure to chemicals of all kinds. Although to my knowledge there are no data on this aspect relating specifically to phthalates, it would surprise me if this fact would not apply to phthalates as well.

Children could be effectively protected from such detrimental effects by eating high quality food with a high redox potential and ingredients replent in free electrons. This goal, however, is seldom achieved for two reasons:

1) despite global overproduction of food, children in many parts of the world are still often undernourished
2) typical industrialized food today provides only about 50% of the redox potential of food produced 50 years ago.

Micronutrient supplements derived from non-industrialized producers, therefore, have become absolutely essential in the treatment of chemically-exposed children.

Exposure avoidance as the basic preventive and essential therapeutic principle in environmental medicine

We can expect that the immunological dysregulation induced by chemicals such as phthalates will be treatable in the future. It is doubtful, however, if the same can be expected for endocrinological dysfunctions. In any case, the continued use of chemicals considered essential by society will create a financial burden on health systems of countries everywhere. The actual extent of this burden, including costs for diagnosis and therapy as well as losses in the work-force by influence on the physical, intellectual, psychological and professional development later on, defies all calculation at the present time.

From the point of view of the most rational and cost-effective environmental medical approach to this problem, the only solution is to simply stop the exposition. Considering, however, the present annual global production of over eight million tons of phthalates and their unhindered use in kindergartens, schools, sport halls, toys and other objects of daily life, the discrepancy between medical dictates and economic reality becomes obvious. While a new approach to registering, evaluating, and authorizing chemicals (the so-called REACH program) is being introduced in the European Union, the basic dilemma remains. Risk estimates will continue to be based on purely toxicological methods, with little consideration of the enzymatic, endocrinological or immunological aspects of individuals, let alone of children.

We environmental physicians, therefore, demand inclusion of the principles outlined here in defining new strategies for prevention of adverse effects by chronic low dose exposure to chemicals and for treating chemically-exposed patients, in particular children, in the future.