

Urinary Tract Diseases Revealed after DTP Vaccination in Infants and Young Children

Cytokine Irregularities and Down-regulation of Cytochrome P-450 Enzymes Induced by the Vaccine May Uncover Latent Diseases in Genetically Predisposed Subjects

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Prophylactic vaccinations may sometimes shorten the incubation period of some illnesses and/or convert a latent infection/inflammation into a clinically apparent disease. Cytokines play a major role in mediating the inflammatory process in various clinical entities and represent a potential source of tissue damage if their production is not sufficiently well controlled. It seems that irregularities in production of proinflammatory cytokines may be responsible for the abnormalities associated with full-blown clinical symptoms of various urinary tract diseases observed after DTP vaccination in 13 infants and young children hospitalized over the past 24 years. On admission, upper respiratory tract diseases, atopic dermatitis, and/or latent urinary tract infection/inflammation were found in these children. It is suggested that the whole-cell pertussis present in DTP vaccine, acting as an excessive stimulus in these patients, produced symptoms reminiscent of biologic responses to circulating proinflammatory monokines such as IL-1 β , TNF- α , and IL-6 because earlier it was reported that in vitro the whole-cell vaccine induced significantly more such cytokine production than did the acellular pertussis or diphtheria-tetanus-only vaccine. Analysis of the cellular immune disturbances previously reported in urinary tract infection/inflammation (increased serum and/or urinary IL-1 α , IL-1 receptor antagonist, IL-6 and IL-8), steroid-sensitive nephrotic syndrome (increased IL-2, IFN- γ , TNF- α , and decreased or increased IL-4, depending on the cells studied), and atopic dermatitis (decreased IFN- γ and increased IL-4 production), may suggest that similar subclinical chronic cytokine-mediated abnormalities produced in the course of latent diseases revealed in our patients, combined with those caused by DTP vaccination stimulus, were responsible for the pathomechanism of these clinical entities. This speculation is in agreement with the reports on the long-lasting induction of cytokine release and down-regulation of hepatic cytochrome P-450 isoenzyme activities after administration of DTP vaccine to mice and may be supported by the fact that T_H1 phenotype is associated with the up-regulation of intercellular adhesion molecule-1 and RANTES, whereas T_H2 phenotype is associated with the up-regulation of the vascular cell adhesion molecule and P-selectin, which are key players in the migration into inflamed tissues and localization of lymphocytes and other allergic effector and inflammatory cells. Because several inflammatory cytokines down-regulate gene expression of major cytochrome P-450 and/or other enzymes with the specific effects on mRNA levels, protein expression, and enzyme activity, thus affecting the metabolism of several endogenous lipophilic substances such as steroids, lipid-soluble vitamins, prostaglandins, leukotrienes, thromboxanes, and exogenous substances, their irregularities in the body may eventually lead to the flare of latent diseases in some predisposed subjects. Also, interleukin genetic polymorphisms, especially the constellation of TNF- α and IL-6 genetic variants, might predispose some infants with infection to a more than usually intense inflammatory response in the kidneys after vaccination. It seems that the aforementioned pathomechanism may also be responsible for some cases of sudden infant death syndrome, which is often preceded by infection/inflammation.

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INTRODUCTION

In 1967, Wilson¹ argued that, in some instances, immunization could shorten the incubation period of some diseases or convert a latent infection/inflammation into clinically apparent disease. The necessary precondition for such an occurrence is the presence of latent infection or asymptomatic colonization. In a cohort of 64,591 children who received a diphtheria and tetanus toxoids and pertussis (DTP) immunization, Griffin et al² identified a total of 158 episodes of invasive bacterial infections, yielding an incidence of 394 infections per 100,000 persons. Eight of these infections occurred within the first 7 days after any DTP immunization, and there were 35 cohort children who had an invasive bacterial infection within 28 days of immunization. In another population-based, case-control study (218,000 children 1–24 months of age; estimated 368,000 DTP immunizations), 424 confirmed cases of neurologic illnesses were identified,³ whereas in a large cohort of 22,505 infants who received a DTa (acellular)P vaccine, 153 serious adverse events were reported, including 7 cases of sudden infant death syndrome (SIDS).⁴ Although Griffin et al² believed that there is no early large increased risk of serious bacterial infections, an association between DTP immunization in the previous 30 days and the occurrence of SIDS was reported,⁵ and a statistical difference between vaccination status of SIDS cases and controls younger than 3 months was found.⁶ Moreover, recent findings from animal and human studies confirmed that DTP vaccination increased the risk of allergies and related respiratory symptoms in children and adolescents^{7,8} and caused reactive arthritis and immunovascularitis with cardiovascular shock⁹ and panarteritis nodosa (after DT vaccination).¹⁰

In Poland, DTP vaccination is recommended in children 2–3 months of age, and 3 doses at approximately 6-week intervals are administered; a booster dose of DTP is given at 19–24 months and boosters of DT at 6 and 14 years.¹¹ During the past 24 years, we observed 13 children of ages 3–65 months who were admitted to the hospital because of full-blown symptoms of urinary tract diseases that developed a few hours to 10 days after the first or subsequent DTP vaccination. Analysis of the cellular immune disturbances that occurred during the subclinical course of the diseases

found in our patients, ie, urinary tract infection (UTI), pyelonephritis, steroid-sensitive nephrotic syndrome (NS), and atopic dermatitis (AD), may suggest that cytokine-mediated abnormalities, coming not only from T-helper (Th) lymphocyte subsets, but also from multiple other leukocytes and even nonhematopoietic cells superimposed on those evoked by the DTP vaccination stress and immunologic stimulus, were responsible for the pathomechanism of these clinical entities and flare of clinical symptoms. The purpose of this work was to present the data that cytokine irregularities induced by the vaccine may uncover latent disease, especially in genetically predisposed subjects.

MATERIALS AND METHODS

Patients

The patient population consisted of 13 children, ages 3–65 months (7 boys, 6 girls), collected over the past 24 years who have been admitted to Korczak Memorial Children's hospital because of different full-blown clinical symptoms a few hours to several days after the first or subsequent DTP vaccination (Table 1).

Methods

The diagnosis of UTI was based on significant bacterial growth in urine (>100,000 colony-forming units/mL) with or without pyuria (>5 white blood cells per high-power field) obtained by fresh and clean midstream voided urine specimens. Febrile UTI was defined as a positive urine culture in a child seen at the emergency department presenting with a fever (>38°C) in whom a urine culture was part of the workup. For each patient, only the first positive urine culture was included.^{12,13} The diagnosis of pyelonephritis was based on clinical, laboratory, ultrasonographic, intravenous urography, and/or cystourethrography data obtained. The criteria for diagnosing NS were those proposed by the International Study on Kidney Disease in Children.¹⁴ All children had standard ultrasonography of the urinary tract performed with the patient in the supine and prone positions within 1–2 days of admission, and, when necessary, some of them had voiding cystourethrography performed according to a standard procedure to detect the vesicoureteral reflux (VUR). The indications for

Table 1. Clinical and laboratory data of children with urinary tract diseases revealed after DTP vaccination

Pt.	Age (mo)/ gender	Patient history/physical examination findings	DTP vaccination dose; time from vaccination to apparent clinical symptoms	Clinical symptoms before admission	Laboratory, ultrasonographic, and voiding cytourethrographic data
1	3/M	Syncope 1 mo earlier	3rd; 5 h	Syncope, tachycardia	ESR 50/h, UTI, pyuria, bilateral VUR
2	3/M	9 pts Apgar, unrest 3 wk earlier, atopic dermatitis	2nd; 8.5 h	Dysuria, unrest, crying, bending legs, fever 38°C, right OM, urethritis, rhino	ESR 21/h; CRP 40.7 mg/L, WBC $22.3 \times 10^9/L$, PLT $536 \times 10^9/L$, serum K ⁺ 5.89 mmol/L, UTI, pyuria
3	4/M	Dysuria from 2 mo, atopic dermatitis	2nd; 4 d	Vomiting, fever 39°C, brown urine	ARF (C _{kr} 30 mL/min), UTI, pyelonephritis, bilateral VUR, BP 160/100 mm Hg, Hb 0.93 mmol/L, WBC $16.2 \times 10^9/L$, pyuria, erythrocyturia
4	4/F	9 pts Apgar, right-sided lower tonus of muscles from 1 mo of age	2nd; 2 h	Edema of legs, dysuria, fever 38°C, unrest, cyanosis from 2 wk during rehabilitation with Vojta method	ESR 15/h, Hb 1.66 mmol/L, WBC $16.8 \times 10^9/L$, PLT $487 \times 10^9/L$, CRP 44.6 mg/L, IgG 0.69 g/L (n = 1.9–8.6); IgM <0.17 g/L (n = 0.25–1.2 g/L), UTI, pyuria
5	5/F	UTI and pyuria at 2 mo of age	3rd; few hours	Vomiting, fever 40°C	ESR 25/h, UTI, left VUR, pyuria
6	5/F	8 pts Apgar	2nd; 10 d	Fever, dysuria, unrest	ESR 5/h, serum K ⁺ 5.88 mmol/L, bilateral VUR, right renal pelvis and ureter duplex, UTI, pyuria
7	5/M	Atopic dermatitis	1st; 6 d	Green, watery stools with mucus	ESR 7/h, UTI, pyuria
8	7/M	Atopic dermatitis, UTI at 3 mo of age	3rd; 4.5 h	Temp. 38.9°C, unrest, groaning, urethritis, rhino, right OM	ESR 20/h, CRP 28.8 mg/L, WBC $15.7 \times 10^9/L$, serum K ⁺ 4.01 mmol/L, UTI, pyuria
9	20/F	8 pts Apgar	2nd; few hours	Temp. 38°C, pharyngitis	ESR 37/h, UTI, pyuria
10	21/M	Purulent tonsillitis twice in the last month	4th; few hours	Edema of the extremities, ascites	ESR 90/h, UTI, pyuria
11	21/F	Purulent tonsillitis	4th; 3 h	Drowsiness, perioral cyanosis	ESR 15/h, UTI, pyuria
12	24/F	Atopic dermatitis	4th; 4 d	Oliguria, and generalized edema	NS with ARF, pyuria
13	65/M	SSNS, atopic dermatitis	5th; 7 d	Pharyngitis	First proteinuria 2.1 g/L, and then full-blown symptoms of SSNS

SSNS, steroid-sensitive nephrotic syndrome; GLN, glomerulonephritis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cells; PLT, platelets; BP, arterial blood pressure; rhino, rhinopharyngitis; OM, otitis media.

reflux examination were ultrasonographically diagnosed dilation of the urinary pelvicaliceal system and sometimes UTI/pyelonephritis. On admission, the arterial blood pressure, hydration state (estimated clinically and with hematocrit value), and kidney function of the patients (blood urea, serum creatinine, C_{kr}), were normal, except for patients 3 and 12 who had clinical and laboratory data characteristic of acute renal failure (ARF).

DTP vaccine

All children received DTP vaccine (reg. no R/0037; Biomed SA, Cracow, Poland) containing 25 Lf of diphtheria toxoid, 10 BU of tetanus anatoxin, and up to 20 billion of *Bordetella pertussis* rods (Cohen-Wheeler semisynthetic breeding-ground culture) killed with formaldehyde, adsorbed onto 0.7 mg aluminium hydroxide; thiomersal was added as a preservative up to 0.01%, and isotonic sodium chloride up to 0.5 mL. This composition of the vaccine was in agreement with the WHO requirements. Analysis of 13.34 children who received 2520 doses of this vaccine showed that only 1 child with concomitant AD and upper respiratory tract infection had postvaccination complications manifested as urosepsis.^{15a}

RESULTS

Patient history, admission physical examination findings, clinical symptoms, and some laboratory data of the patients are presented in Table 1. Eight of 13 patients were infants 3–7 months old (5 boys, 3 girls), 4 other children were of ages 20–24 months and 1 child was 65 months old. On admission, 4 of 13 children had a decreased Apgar score at birth, 6 had AD, 2 had purulent tonsillitis, and 8 children already manifested different clinical symptoms 3 weeks to a few months before hospitalization (patients 3, 5, and 8 had clinical symptoms of the underlying urinary tract disease 2–5 months before admission, and patient 13 had remission of NS and was not receiving prednisone).

Almost all children had UTI and pyuria. In patient 7, UTI and pyuria were observed 6 days after the first DTP injection, 5 other children had clinical symptoms after the second vaccination, whereas other patients became ill after the third or fourth dose of DTP vaccine. Patient 13 with NS and AD had pronounced proteinuria after the fifth dose of DTP, and during the next few days, he showed all the characteristic clinical and biochemical symptoms of relapsing steroid-sensitive NS.

Eight of 13 children showed clinical symptoms of disease 2–8.5 hours after DTP vaccination, and in other patients, it took 4–10 days before the symptoms started to manifest. In patients 1 and 11, the clinical symptoms were very serious, resembling shock. In patients 1 and 5, voiding cystourethrography showed the presence of VUR; despite that, pyuria was not very pronounced.

The majority of the patients presented with laboratory results indicating an advanced inflammatory process taking its course after DTP vaccination (8 of 13 children had increased erythrocyte sedimentation rate, 4 of 13 and 2 of 13 patients had leukocytosis and/or increased platelet counts, respectively, and 3 of 13 children had an increased serum C-reactive protein concentration. Patient 9 had marked immunologic abnormalities: phagocytosis, 67% ($n = 90\%–100\%$); early T lymphocytes, 38% ($n = 25–40$); late T lymphocytes, 65% ($n = 70–80$); B lymphocytes, 34% ($n = 20\%–30\%$); total number of T lymphocytes, 1099 cells/mm³ ($n = 1350–5915$); total number of B lymphocytes, 575 cells/mm³ ($n = 550–1690$).

Patient 3 was strikingly pale on admission, and his laboratory results were characteristic of ARF (blood urea, 88 mg/dL; serum creatinine, 101.7 μ mol/L), which developed in the course of acute pyelonephritis (confirmed by intravenous urography), and bilateral VUR. After 7 days of treatment, proteinuria, erythrocyturia, and pyuria ceased, and his C_{kr} increased from 30 to 41 mL/min. The patient's laboratory data and arterial blood pressure became normal after 3 weeks of therapy, and he was discharged home.

In patient 12, oliguria was observed on the fourth day after DTP vaccination, and she was hospitalized 3 days later. On admission, the girl was in a poor condition; her BP was 130/95 mm Hg, and her clinical symptoms and laboratory results met the criteria of renal insufficiency and full-blown NS. Histopathologic abnormalities found in the renal biopsy specimen were characteristic of minimal change NS or proliferative glomerulonephritis in the phase of recovery. After 7 days of treatment with prednisone, proteinuria ceased, and the symptoms of renal insufficiency disappeared. Her biochemical data normalized by the sixth week, and after 9 weeks of hospitalization, the child returned home.

DISCUSSION

In our patients, the first or subsequent DTP vaccination revealed latent UTI with or without VUR, pyelonephritis, sometimes complicated by ARF, and/or NS.

Some patients already had clinical symptoms of the underlying urinary tract disease 2–5 months before hospitalization; a few were vaccinated while having an upper respiratory tract disease. Many of them had clinical symptoms of AD, and 4 had a decreased Apgar score. Urine examination on admission showed that almost all children had UTI and pyuria. The development of urinary tract diseases after the vaccination may be a coincidence in our patients, yet the timing strongly favors immune-mediated side effects of vaccination, especially that cytokine-mediated abnormalities in lymphocyte, monocyte, and/or other cell functions were reported in all these clinical entities and after DTP vaccination.

DTP vaccination and production of cytokines and down-regulation of liver cytochrome P-450 activities

The pathophysiology of adverse clinical events sometimes occurring after DTP vaccination is not well understood. Active pertussis toxin in DTP vaccine has been proposed to induce these severe reactions. In animal models, large doses of pertussis toxin caused hyperinsulinemia and hypoglycemia as well as leukocytosis with a predominant lymphocytosis.¹⁵ In 56 children who experienced severe reactions after DTP immunization, leukocytosis with neutrophilia were also observed acutely compared with follow-up performed approximately 1 month later.^{16,17} Because cytokines play a major role in mediating the inflammatory process in various clinical entities¹⁸ and also represent a potential source of tissue damage if their production is not sufficiently well controlled, it is possible that they may also provide a key to the understanding of these abnormalities. It is known that the immunoregulatory cytokines IL-2, IFN- γ , and TNF- β constitute the type 1 (T_H1) cytokine response, and the cytokines IL-4, IL-5, IL-6, IL-8, IL-10, and IL-13 constitute the type 2 (T_H2) cytokine response.¹⁹ Blood-Siegfried et al²⁰ suggested that whole-cell pertussis present in DTP vaccine can produce symptoms reminiscent of biologic responses to circulating proinflammatory monokines such as IL-1 β , TNF- α , and IL-6, and found that in vitro whole-cell vaccine induced significantly increased production of these cytokines than did the acellular pertussis or diphtheria-tetanus-only vaccine. They suggested that although pertussis endotoxin was a major inducer of IL-6, other components of *B. pertussis* also contributed to this cytokine production by monocytes.²⁰ In other studies performed on infants, antigen-stimulated peripheral blood mononuclear cells of responsive whole-cell pertussis vaccine recipients were characterized by el-

evated production of IFN- γ (which inhibits the growth of T_H2 cells) and IL-2, low to minimal production of IL-5, and no production of IL-4.^{21,22} Absence of type 2 cytokines and low levels of constitutive IFN- γ production were reported in prevaccination children.²¹ Studies in mice showed that the administration of whole-cell DTP vaccine caused dose- and time-dependent marked increases in the hepatic mRNA expression of IL-6, IL-1, and TNF as well as a significant depression for about 7 days in the expression of mRNA and activities of liver isoenzymes of cytochrome P-450.^{23–26} Both spleen and liver weights in mice were increased for 7–14 days after DPT vaccination, and histopathologic tissue examination showed random multifocal inflammation with hepatocyte necrosis.²⁶ DTP vaccine also caused marked induction of IFN- γ coincident with the maximal inhibition of CYP-450 levels²⁵ and increased inducible nitric oxide synthase mRNA expression, claimed by some authors as being responsible for the down-regulation of cytochrome P-450 enzymes.²⁷ Finally, it must be added that DTP vaccination is usually accompanied by stress reactions^{16,17} in which there is an increased level of circulating adrenaline and corticosteroids followed by an elevated plasma concentration of IL-6.^{28–33} Since IL-6 has the acute phase protein nature^{28,33} and manifold biologic functions involved in the immune and inflammatory responses of the host to various stimuli,^{18,19} it is likely that this proinflammatory cytokine increased production is associated with disturbances of homeostasis, such as an excessive intensity of inflammatory reactions of our patients both to injection of the vaccine and a latent infection/inflammation.^{32,34}

UTI and/or pyelonephritis

All our patients had underlying latent UTI, VUR, and/or pyelonephritis, and it is known that bacteria causing UTI infection stimulate an inflammatory response in the individual. IL-6 and IL-8 have been found in increased concentrations in the serum and urine of children and adults with UTI and asymptomatic bacteriuria.^{35,36} During the acute phase of UTI, IL-6 serum levels increased markedly in these children who later developed chronic pyelonephritis compared with those who did not show any renal damage on scintigraphy at the time of establishing a diagnosis.³⁷ Moreover, other studies^{35,38,39} showed that in children with febrile UTI and pyelonephritis, urinary IL-6 and IL-8 concentrations were elevated (as well as IL-1 α and IL-1ra, IL-1 receptor antagonist⁴⁰) compared with controls and statistically correlated with urine white blood cells³⁸; higher IL-8 values were observed in patients with pyelonephritis who were younger than 1

year of age.³⁹ The magnitude of urinary IL-8 response was associated with hemolysin production, a bacterial virulence factor of *Escherichia coli*. All these data indicate that IL-6 and IL-8 may be mediators of inflammation in children with febrile UTI.³⁸ An abnormal production of IL-6 has been suggested to be involved in the pathogenesis of a variety of diseases, such as mesangial proliferative glomerulonephritis, rheumatoid arthritis, and several autoimmune diseases.⁴¹ This acute phase cytokine (known also as IFN- β_2) is produced early in inflammation by fibroblasts, monocytes, and other cells (shortly after IL-1 and TNF- α) and displays several proinflammatory properties (eg, maturation and activation of neutrophils, increased expression of IL-1 and TNF- α).^{18,42} Leukocyte proteinase, in turn, can degrade connective tissue proteins and may also be involved in other processes including inflammatory reactions.⁴³⁻⁴⁵ The biosynthetic activity of neutrophils must also be considered an important source of cytokines during acute infection since they may comprise up to 70% of the circulating pool of leukocytes. The other cytokine, IL-8, is produced by macrophages (together with IL-1, IL-6, and TNF- α) and endothelial cells soon after infection or tissue injury, and it was found that neutrophils not only respond to IL-8 but also are capable of synthesizing IL-8 and other chemokines under the appropriate conditions.¹⁸ Finally, it must be added that the constellation of TNF- α and IL-6 genetic variants might lead to an enhanced inflammatory response in the kidneys, sometimes resulting in ARF, especially in infants with infection.⁴⁶

Nephrotic syndrome

Various lymphokines have been implicated in the pathophysiology of NS. NS is frequently associated with allergic symptoms such as AD, bronchial asthma, allergic rhinitis, urticaria, eczema, hayfever, poison ivy, pollen hypersensitivity, and elevated serum IgE levels and IL-4, with the IgE correlating with IL-4 levels and the degree of proteinuria correlating with the IL-4 concentration.^{47,48} Relapse is frequently preceded by immunologic stimuli, including viral infections, vaccinations (DTP/hepatitis B vaccine), and bee stings,⁴⁹⁻⁵² which would stimulate sensitized lymphocytes to produce a number of highly active cytokines causing an imbalance of circulating humoral factors.⁵³⁻⁵⁸ In the supernatants of CD4⁺ T-cell cultures obtained from children with NS aged 2-9 years (at this age, the immune response is strictly dependent on the activity of the thymus) and stimulated by autologous monocytes presenting tetanus toxoid, Stachowski et al⁵⁹ found decreased synthesis of IL-2, IL-10, and IFN- γ compared with healthy controls. Other authors

who investigated patients 2-15 years old also reported cytokine-mediated abnormalities in lymphocyte and monocyte function, such as an increase in the number and function of T_H1 cells producing large amounts of IL-2 and IFN- γ , while IL-8 levels were decreased,^{53,55} demonstrated elevated levels of IL-2, IL-4, and IFN- γ ⁵⁴ or found a decreased release of IL-10 by monocytes.⁶⁰ Also, a marked increase in serum TNF- α in patients with NS has been reported.^{61,62} All these cytokine abnormalities may have clinical consequences because, for example, IL-2 induces production of IFN- γ and TNF- β , which results in activation of monocytes, neutrophils, and natural killer cells, while IL-10 inhibits proinflammatory cytokine production by activated monocytes/macrophages and has a potent stimulatory effect on B cells, especially with respect to antibody production.¹⁸ Moreover, IFN- γ promotes T_H1 responses and inhibits T_H2 responses, and its priming and activation of macrophages lead to enhanced production of proinflammatory cytokines in response to several stimuli.¹⁸ On the other hand, long-term remission of NS appears to be related to increased T_H2 cytokine production, down-regulating T_H1 cytokines and cytotoxic cells.⁵⁵

Falus et al⁶³ suggested that a local tissue imbalance in the ratio of IL-1, IL-6, and TNF- α in different pathologic cases might influence the sensitivity of lymphocytes, monocytes, and hepatocytes as target cells to glucocorticosteroids. The inflammatory cytokines IL-1, IL-6, and TNF- α cause an increase in glucocorticosteroid binding in human lymphoid, monocytoid, and hepatoma cell lines and markedly increased the level of glucocorticosteroid receptors.⁶⁴ The study by Ramirez et al⁶⁵ showed that the exposure of the purified rat CD4⁺ cells to glucocorticosteroids promoted the T_H2 response (ie, increased mRNA levels of IL-4, IL-10, and IL-13), whereas inhibited the T_H1 response (the synthesis of IFN- γ and TNF- α was decreased). Moreover, it appeared that IL-4 potentiated the effect of dexamethasone,⁶⁵ while IL-2 production may be inhibited by an excess of IL-4 and IL-10.⁵⁹ One may, therefore, suggest that chronic exposition to prolonged UTI infection and atopic inflammation may sometimes lead to a serious T_H1/T_H2 cytokine imbalance in the body and result in a diminished levels of endogenous corticosteroids because of increased requirements and metabolic turnover of these important endogenous substances, finally revealing NS in a genetically predisposed subject.⁶⁶ This may be supported by the fact that several inflammatory cytokines down-regulate gene expression of major cytochrome P-450 and/or other enzymes with the specific effects on mRNA levels, protein expression, and

enzyme activity, thus affecting the metabolism of several endogenous lipophilic substances, such as steroids, lipid-soluble vitamins, prostaglandins, leukotrienes, thromboxanes, growth hormone, and exogenous substances.⁶⁷⁻⁶⁹

Atopic dermatitis

Exposure to microbial stimuli during early childhood can influence the induction and expression of atopic disease.⁷⁰ In virtually all newborn infants, they are polarized toward T_H2 responses to common environmental allergens, comprising IL-4, IL-5, IL-6, IL-9, and IL-13, and are dominated by a high level of production of IL-10.⁷¹ This T_H2 polarization may be more pronounced and long-lasting in children with the atopic genotype. The failure of this immune-deviation process is associated with decreased capacity to produce the T_H1 cytokine IFN- γ ,⁷² which is much lower in fetal T cells than in adults and increases progressively from birth to 5 years of age,⁷³ when compartmentalization of allergen-specific T-cell immunity into adult-equivalent T_H1 rather than T_H2 patterns occurs in most children.⁷⁴ Decreased IFN- γ and increased IL-4 production reported in atopics may contribute to increased IgE synthesis and eosinophilia characteristic of this clinical entity.⁷⁵ In contrast, nonatopic people show mainly T_H1 immunity characterized by production of IFN- γ , which is known to inhibit the growth of T_H2 cells.⁷² It must be emphasized that the increased production of IL-4 found in patients with AD⁷⁵ may also indicate that the protracted inflammatory and immunologic processes are running their course in these patients because it is known that this cytokine has the striking ability to suppress many monocyte proinflammatory responses such as IL-1 β , TNF- α and - β , IL-6, and IFN- γ .^{18,76,77}

In AD, the expression of T_H2 -skewed immunity against antigens present in the normal environment is recognized as the primary cause of allergic inflammation. DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents.⁷ Recent findings suggest that a hallmark of the atopic phenotype is the reduced capacity to respond to vaccine antigens as well as environmental allergens during infancy. This deficiency, which is most marked for IFN- γ , appears transient but can result in a long-lasting imbalance within T-helper cell memory responses to allergens.⁷⁸ Prescott et al⁷² measured mononuclear cell proliferative and cytokine responses to specific allergens and TT in blood samples from atopic and nonatopic infants every 6 months from birth to 2 years of age. Samples from 18 atopic and 13 nonatopic infants showed low-level, T_H2 -skewed, allergen-specific responses at birth, with

little accompanying specific IFN- γ production. In the atopic group, neonatal T_H2 responses were significantly lower for IL-4, IL-6, IL-10, and IL-13 than in the nonatopic group. There was rapid suppression of T_H2 responses during the first year of life in nonatopic children, but there was consolidation of responses in atopic children associated with defective neonatal IFN- γ production. It is believed that the continuation of fetal allergen-specific T_H2 responses during infancy is a defining feature of the inductive phase of atopic disease and is associated with a decreased capacity for the production of the T_H1 cytokine IFN- γ by atopic neonates.⁷² Also, it appeared that peripheral blood mononuclear cells from the atopic 6-year-old children produced higher levels of T_H1 and T_H2 cytokines to house dust mite antigens and phytohemagglutinin (mitogen).⁷⁸ Recently, it was reported that T_H0/T_H2 -type responses predominate in the skin of patients with AD, and high levels of soluble CD30 were detected in the serum that correlated with disease activity.⁷⁹ Because CD30 is a member of the TNF receptor family, which is preferentially expressed by T cells producing T_H2 -type cytokines,⁸⁰ it may indicate that excessive signaling leading to enhanced production of proinflammatory mediators cause chronic allergic inflammatory reactions and tissue injury in these patients.

Summary

It seems that in some young children with upper respiratory tract infection and/or AD, DTP vaccination acting as an excessive stimulus may convert a latent urinary tract disease into an apparent illness because of the chronic migration of helper T-lymphocyte subsets into inflamed tissues⁷⁴ and steady enhanced production of proinflammatory cytokines that result in a local cytokine milieu imbalance leading to subclinical, sometimes allergic, protracted inflammation and enhanced bacterial growth and finally to the flare of disease symptoms. This scenario is in agreement with the reports on the induction of cytokine release and depression of hepatic mRNA levels of cytochrome P-450 isoenzymes after administration of DTP vaccine to mice²³⁻²⁶ (similar abnormalities were suggested previously to act as triggering factors in eliciting also several other diseases⁶⁷⁻⁶⁹) and may be supported by the fact that T_H1 phenotype is associated with the up-regulation of intercellular adhesion molecule-1 and RANTES, whereas T_H2 phenotype is associated with the up-regulation of vascular cell adhesion molecule and P-selectin, known as the key players in tissue localization of lymphocytes and other allergic effector cells.⁸¹ Finally, genetic polymorphisms of TNF- α and IL-6 may also predispose some infants with infection

to a more than usually intense inflammatory response in the kidneys after vaccination.⁴⁶ Polymorphism in some genes of the host immune system is associated with susceptibility to infections and, in contrast, using vaccines as probes of the immune system is a novel means of identifying disease susceptibility genes.⁸²

REFERENCES

1. Wilson GS. Indirect effects: provocation disease. In: *The hazards of immunization*. London: The Athlone Press; 1967:265–280.
2. Griffin MR, Taylor JA, Daugherty JR, et al. No increased risk for invasive bacterial infection found following diphtheria-tetanus-pertussis immunization. *Pediatrics*. 1992;89:640–642.
3. Gale JL, Thapa PB, Wassilak SG, et al. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. *JAMA*. 1994;271:37–41.
4. Schmitt HJ, Schuind A, Knuf M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. *J Pediatr*. 1996;129:695–701.
5. Caro-Paton T, Carvajal A, Lobato A, et al. DTP vaccine and sudden infant death syndrome. Is there any relationship? A meta-analysis. Abstracts of the 1st Congress of the European Association for Clinical Pharmacology and Therapeutics, Paris, France, September 27–30, 1995. *Therapie*. 1995;50(suppl 1):abstr 178.
6. Jonville-Bera AP, Autret E, Laugier J. Sudden infant death syndrome and diphtheria-tetanus-pertussis-poliomyelitis vaccination status. *Fundam Clin Pharmacol*. 1995;9:263–270.
7. Hurwitz EL, Morgenstern H. Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Ther*. 2000;23:81–90.
8. Kemp T, Pearce N, Fitzharris P, et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology*. 1997;8:678–680.
9. Wiersbitzky S, Bruns R, Niendorf A. Pediatric vaccination advice: reactive arthritis and immuno-vasculitis with cardiovascular shock following triple prophylactic vaccination (diphtheria-pertussis-tetanus). *Kinderarztl Prax*. 1990;58:547–549.
10. Domula E, Petter O. Panarteritis nodosa after diphtheria-tetanus vaccination and influence of gluten containing nutritive factors. *Z Haut Geschelchskr*. 1970;45:655–661.
11. Torbicka E, Lagergard T, Trollfors B. Serum antibodies to the components of diphtheria-tetanus-pertussis vaccine in Polish children related to vaccination status. *Infection*. 1995;23:212–215.
12. Larcombe J. Urinary tract infection in children. *BMJ*. 1999;319:1173–1175.
13. Vickers D, Ahmad T, Coulthard MG. Diagnosis of urinary tract infection in children: fresh urine microscopy or culture? *Lancet*. 1991;338:767–770.
14. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int*. 1978;13:159–165.
15. Munoz JJ, Arai H, Bergman RK, et al. Biological activities of crystalline pertussin from *Bordetella pertussis*. *Infect Immun*. 1981;33:820–826.
- 15a. Adonajlo A, Plucinska E, Kozerska D, et al. Reactions to vaccination and serologic response to the pertussis component of diphtheria-tetanus-pertussis (DiTePer) vaccines in children. *Przegl Epidemiol*. 872;26:453–464.
16. Blumberg DA, Lewis K, Mink CM, et al. Severe reactions associated with diphtheria-tetanus-pertussis vaccine: detailed study of children with seizures, hypotonic-hyporesponsive episodes, high fevers, and persistent crying. *Pediatrics*. 1993;91:1158–1165.
17. Blumberg DA, Mink CM, Lewis K, et al. Pathophysiology of reactions associated with pertussis vaccine. *Dev Biol Stand*. 1991;73:289–295.
18. Curfs JHAJ, Meis JFGM, Hoogkamp-Korstanje JAA. A primer on cytokines: sources, receptors, effects and inducers. *Clin Microbiol Rev*. 1997;10:742–780.
19. Lucey DR, Clerici M, Shearer GM. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. *Clin Microbiol Rev*. 1996;9:532–562.
20. Blood-Siegfried J, Crabb Breen E, Takeshita S, et al. Monokine production following in vitro stimulation of the THP-1 human monocytic cell line with pertussis vaccine components. *J Clin Immunol*. 1998;18:81–88.
21. Ausiello CM, Urbani F, la Sala A, et al. Vaccine- and antigen-dependent type 1 and type 2 cytokine induction after primary vaccination of infants with whole-c or acellular pertussis vaccines. *Infect Immunol*. 1997;65:2168–2174.
22. Ryan M, Murphy G, Ryan E, et al. Distinct T-cell subtypes induced with whole cell and acellular pertussis vaccines in children. *Immunology*. 1998;93:1–10.
23. Ansher SS, Thompson W. Modulation of hepatic mRNA levels after administration of lipopolysaccharide and diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP vaccine) to mice. *Hepatology*. 1994;20:984–991.
24. Fantuzzi G, Sironi M, Delgado R, et al. Depression of liver metabolism and induction of cytokine release by diphtheria and tetanus toxoids and pertussis vaccines: role of *Bordetella pertussis* cells in toxicity. *Infect Immun*. 1994;62:29–32.
25. Ansher S, Thompson W, Bridgewater J, et al. Pertussis toxin-induced alterations of murine hepatic drug metabolism following administration of diphtheria and tetanus toxoids and pertussis vaccine adsorbed. *Infect Immun*. 1993;61:4240–4247.

26. Ansher S, Thompson W, Snoy P, et al. Role of endotoxin in alterations of hepatic drug metabolism by diphtheria and tetanus toxoids and pertussis vaccine absorbed. *Infect Immun.* 1992;60:3790–3798.
27. Morgan ET. Regulation of cytochrome P450 by inflammatory mediators: why and how? *Drug Metab Dispos.* 2001;29:207–212.
28. Van Gool J, van Vugt, Helle M, et al. The relation among stress, adrenalin, interleukin 6 and acute phase proteins in the rat. *Clin Immunol Immunopathol.* 1990;57:200–210.
29. DeRijk RH, Boelen A, Tilders FJ, et al. Induction of plasma interleukin-6 by circulating adrenalin in the rat. *Psychoneuroendocrinology.* 1994;19:155–163.
30. Dantzer R, Kelley KW. Stress and immunity: an integrated view of relationships between the brain and the immune system. *Life Sci.* 1989;44:1995–2008.
31. Zhou D, Kusnecov AW, Shurin MR, et al. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. *Endocrinology.* 1993;133:2523–2530.
32. Huang QH, Takaki A, Arimura A. Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. *Am J Physiol.* 1997;273:R731–R738.
33. Ueno Y, Takano N, Kanegane H, et al. The acute phase nature of interleukin 6: studies in Kawasaki disease and other febrile illnesses. *Clin Exp Immunol.* 1989;76:337–342.
34. Dunn AJ. Role of cytokines in infection-induced stress. *Ann N Y Acad Sci.* 1993;697:189–202.
35. Benson M, Jodal U, Agace W, et al. Interleukin (IL)-6 and IL-8 in children with febrile urinary tract infection and asymptomatic bacteriuria. *J Infect Dis.* 1996;174:1080–1084.
36. Jacobson SH, Hylander B, Wretling B, et al. Interleukin-6 and interleukin-8 in serum and urine in patients with acute pyelonephritis in relation to bacterial-virulence-associated traits and renal function. *Nephron.* 1994;67:172–179.
37. Rodriguez LM, Marugan JM, Suarez A, et al. Interleukin 6 (IL-6) serum levels during urinary tract infection (UTI), and prediction of the risk of chronic pyelonephritis. *Pediatr Nephrol.* 2001;16:C17(abstr).
38. Jantusch BA, O'Donnell R, Wiedermann BL. Urinary interleukin-6 and interleukin-8 in children with urinary tract infection. *Pediatr Nephrol.* 2000;15:236–240.
39. Tullus K, Fituri O, Burman L, et al. Interleukin-6 and interleukin-8 in the urine of children with acute pyelonephritis. *Pediatr Nephrol.* 1994;8:280–284.
40. Tullus K, Fituri O, Burman LG, et al. Interleukin 1 α and interleukin-1 receptor antagonist in the urine of children with acute pyelonephritis. *Acta Paediatr.* 1996;85:158–162.
41. Tafuto S, Silvestri I, D'andrea P, et al. Interleukin-6: biological features and clinical implications. *Agents.* 1994;8:1–8.
42. Koj A, Magielska-Zero, Bereta J, et al. The cascade of inflammatory cytokines regulating synthesis of acute phase proteins. *Tokai J Exp Clin Med.* 1988;13:255–264.
43. Travis J. Structure, function, and control of neutrophil proteinases. *Am J Med.* 1988;84(suppl 6A):37–42.
44. Prandota J, Pankow-Prandota L, Kotecki L, et al. Plasma proteinase inhibitor activity and hemostasis tests in children with nephrotic syndrome. Effect of prednisone alone and prednisone plus ϵ -aminocaproic acid treatment regimens: preliminary report. *Am J Ther.* 2001;8:97–107.
45. Prandota J, Pankow-Prandota L, Kotecki L. Impaired activation of the fibrinolytic system in children with Henoch-Schönlein purpura: beneficial effect of hydrocortisone plus ϵ -aminocaproic acid therapy on disappearance rate of cutaneous vasculitis and fibrinolysis. *Am J Ther.* 2001;8:11–19.
46. Treszl A, Toth-Heyn P, Kocsis I, et al. Interleukin genetic variants and the risk of renal failure in infants with infection. *Pediatr Nephrol.* 2002;17:713–717.
47. Arkwright PD, Clark G. Infantile nephrotic syndrome and atopy. *Pediatr Nephrol.* 1996;10:509–510.
48. Yao Z. The production and significance of interleukin-4 in patients with idiopathic nephrotic syndrome. *Chung Hua I Hsueh Tsa Chih (Taipei).* 1993;73:261–263.
49. Prandota J. Two cases of acute renal failure in children after DTP vaccination. *Pediatrics Pol.* 1978;53:215–217.
50. Prandota J, Jarlinska M. Early renal complications following Di-Te-Per vaccination. *Przegląd Pediatr.* 1996;26:435–439.
51. Blowey DL. Nephrotic syndrome associated with an Epstein-Barr virus infection. *Pediatr Nephrol.* 1996;10:507–508.
52. MacDonald NE, Wolfish N, McLaine P, et al. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr.* 1986;108:378–382.
53. Schnaper HW. Primary nephrotic syndrome of childhood. *Curr Opin Pediatr.* 1996;8:141–147.
54. Niehaus TJ, Wadhwa M, Callard R, et al. Increased IL-2, IL-4 and interferon-gamma (INF-gamma) in steroid-sensitive nephrotic syndrome. *Clin Exp Immunol.* 1995;100:475–479.
55. Daniel V, Trautmann Y, Konrad M, et al. T-lymphocyte populations, cytokines and other growth factors in serum and urine of children with idiopathic nephrotic syndrome. *Clin Nephrol.* 1997;47:289–297.
56. Islek I, Cengiz K, Cakir M, et al. Nephrotic syndrome following hepatitis B vaccination. *Pediatr Nephrol.* 2000;14:89–90.
57. Szajner-Milart I, Zajackowska M, Zinkiewicz Z. Clinical and epidemiological evaluation of preventive vaccinations in children with nephrotic syndrome. Abstracts of the 25th Congress of Polish Pediatricians, September 17–20, 1997, Wrocław, Poland, p. 371.
58. Rytznad DA. Onset of the nephrotic syndrome during a reaction to bee sting. *Stanford Med. Bull.* 1995;13:224–233.
59. Stachowski J, Barth C, Michałkiewicz J, et al. Th1/Th2 balance and CD45-positive T cell subsets in primary nephrotic syndrome. *Pediatr Nephrol.* 2000;14:779–785.

60. Matsumoto K. Decreased release of IL-10 by monocytes from patients with lipoid nephrosis. *Clin Exp Immunol*. 1995;102:603–607.
61. Suranyi MG, Guasch A, Hall BM, et al. Elevated levels of tumor necrosis factor- α in the nephrotic syndrome in humans. *Am J Kidney Dis*. 1993;21:251–259.
62. Salsano ME, Luongo I, Piscitelli A, et al. Soluble interleukin-2 receptor and tumor necrosis factor- α in nephrotic syndrome. *Pediatr Nephrol*. 2000;14:C66(abstr P79).
63. Falus A, Biro J, Rakasz E. Cytokine networks and corticosteroids receptors. *Ann N Y Acad Sci*. 1995;762:71–77.
64. Rakasz E, Gal A, Biro J, et al. Modulation of glucocorticosteroid binding in human lymphoid, monocytoid and hepatoma cell lines by inflammatory cytokines interleukin (IL)-1 β , IL-6 and tumor necrosis factor (TNF)- α . *Scand J Immunol*. 1993;37:684–689.
65. Ramirez F, Fowell DJ, Puklavec M, et al. Glucocorticoids promote a Th2 cytokine response by CD4 $^{+}$ cells in vivo. *J Immunol*. 1996;156:2406–2412.
66. Noyan A, Karabay Bayazit A, Bayazit Y, et al. HLA antigens in nephrotic syndrome. *Pediatr Nephrol*. 1999;13: C60(abstr P127).
67. Prandota J. Viral infections and resulting inhibition of xenobiotic metabolizing enzymes as the possible cause of autoimmune hepatitis in a genetically predisposed person persistently exposed to harmful environmental factor(s) [letter]. *Autoimmunity*. 2001;34:155–156.
68. Prandota J. Important role of prodromal viral infections responsible for inhibition of xenobiotic metabolizing enzymes in the pathomechanism of idiopathic Reye's syndrome, Stevens-Johnson syndrome, autoimmune hepatitis, and hepatotoxicity of the therapeutic doses of acetaminophen used in genetically predisposed persons. *Am J Ther*. 2002;9:149–156.
69. Prandota J. Possible pathomechanism of autoimmune hepatitis. *Am J Ther*. 2003;10:51–57.
70. Holt PG, Macaubas C, Prescott SL, et al. Microbial stimulation as an aetiological factor in atopic disease. *Allergy*. 1999;54:12–16.
71. Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the human immune system to environmental allergens; universal skewing of initial t cell responses toward the Th2 cytokine profile. *J Immunol*. 1998;160: 4730–4737.
72. Prescott SL, Macaubas C, Smallacombe T, et al. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet*. 1999;353:196–200.
73. Holt PG. Postnatal maturation of immune competence during infancy and early childhood. *Pediatr Allergy Immunol*. 1995;6:59–70.
74. Yabuhara A, Macaubas C, Prescott SL, et al. Th2-polarized immunological memory to inhalant allergens in atopics is established during infancy and early childhood. *Clin Exp Allergy*. 1997;27:1261–1269.
75. Jujo K, Renz H, Abe J, et al. Decreased interferon gamma and increased interleukin-4 production in atopic dermatitis promotes IgE synthesis. *J Allergy Clin Immunol*. 1992; 90:323–331.
76. Lee JD, Rhoades K, Economou JS. Interleukin-4 inhibits the expression of tumor necrosis factors α and β , interleukin-1 β and -6 and interferon- γ . *Immunol Cell Biol*. 1995;73:57–61.
77. Loyer P, Ilyin G, Abdel Razzak Z, et al. Interleukin 4 inhibits the production of some acute-phase proteins by human hepatocytes in primary culture. *FEBS Lett*. 1993; 336:215–220.
78. Holt PG, Rudin A, Macaubas C, et al. Development of immunologic memory against tetanus toxoid and perac-tin antigens from the diphtheria-tetanus-pertussis vaccine in atopic versus nonatopic children. *J Allergy Clin Immunol*. 2000;105:1117–1122.
79. Caproni M, Bianchi B, D'Elios MM, et al. In vivo relevance of CD30 in atopic dermatitis. *Allergy*. 1997;52: 1063–1070.
80. D'Elios MM, Romagnani P, Scaletti C, et al. In vivo CD30 expression in human diseases with predominant activation of Th2-like cells. *J Leukoc Biol*. 1997;61:539–544.
81. Lukacs NW. Migration of helper T-lymphocytes subsets into inflamed tissues. *J Allergy Clin Immunol*. 2000;106: 264–269.
82. Hayney MS. Pharmacogenomics and infectious diseases: impact of drug response and applications to disease management. *Am J Health Syst Pharm*. 2002;59:1626–1631.