

Hypersensitivity reactions to food additives

M. HANNUKSELA¹ & T. HAAHTELA²

¹Dept. of Dermatology, University of Oulu, Oulu and ²Dept. of Pulmonary Diseases, Kanta-Häme Central Hospital, Hämeenlinna, Finland

Only seldom have food additives been shown to cause true allergic (immunological) reactions. Adverse effects due to various pharmacological or other mechanisms are much more common. The individual tolerance may be decreased for one reason or another, and may fluctuate from time to time. Many patients suffering from food additive reactions have atopic constitutions and such clinical symptoms as flexural dermatitis, rhinitis and asthma. The most important skin symptoms caused by food additives are urticaria, angioneurotic edema, and contact urticaria. Azo dyes, benzoic acid and several other common food additives may aggravate or, more rarely, even cause urticaria. Spices are one of the most common causes of immunological contact urticaria. Non-immunological contact urticaria is produced by numerous spices, benzoic acid, sorbic acid, cinnamic acid, and many essential oils. Asthma and rhinitis are the main hypersensitivity symptoms in the respiratory tract, and azo dyes, benzoic acid, and sulfite food additives are the most common causative agents. Systemic and respiratory reactions to food colorants and benzoates have been claimed to occur more frequently in acetylsalicylic acid- (ASA-)sensitive patients than in non-reactors. Hypersensitivity reactions in organs other than the skin and respiratory tract are rare or poorly documented. Psychological factors play an essential role in both food and food additive reactions.

Key words: food additives; immediate allergy; intolerance.

Accepted for publication 1 May 1987

DEFINITIONS. PREVALENCE OF HYPERSENSITIVITY REACTIONS

Strictly speaking, *allergy* means a harmful physiological reaction caused by *immunological mechanism*. If the mechanism is not an allergic one but the reaction resembles allergic reaction, the term *intolerance* is often used. The symptoms mimic those seen in real allergic reactions but the amount of agent producing the reaction is small enough not to cause a *toxic reaction*. When the mechanism is not known, it is better to talk about *hypersensitivity*, which can mean both allergic reaction and intolerance.

Many authors avoid the use of the terms *allergy* and *atopy* in connection with food additive reactions and prefer *hypersensitivity* or *intolerance* instead. Terms such as *false allergies* (101) have been suggested. All these definitions emphasize the non-specific, non-immunological nature of these reactions.

The prevalence of hypersensitivity reactions to food additives has been estimated to be 0.03–0.15 % in the whole population (26, 68, 100, 116). Juhlin (68) estimated that 30–50 % of patients with chronic urticaria react to one or more food additives. Farr et al. (38) reached the conclusion that 4–6 % of acetylsalicylic acid- (ASA-)sensitive asthmatics react to tartrazine. Sulfite-induced asthma is thought to affect 5–10 % of asthmatics. (19, 137). Weber et al. (152) estimated that bronchoconstriction provoked by food dyes and preservatives occurs in about 2 % of all asthmatics.

One to two per cent of adult patients with hay fever and asthma have experienced harmful symptoms from spices. (36). Immediate skin test reactions to spices are seen in 20 % of atopic patients, especially in those with birch pollen allergy (108).

Many salad dressings contain benzoic acid or

sorbic acid sufficient to elicit contact urticaria on the lips and oral mucosa. Most of us have noticed the "fresh" feeling in the mouth after using mouth washes and tooth pastes and after eating spiced food. This feeling is nothing but non-immunological contact urticaria. Such reactions can thus often be desirable rather than harmful.

MECHANISMS

Immunological reactions to food additives

Some low molecular weight additives can act as haptens and convert to allergens only after they bind to some carrier protein (22). Azo dyes, in particular, have been suggested to act in this way. The same phenomenon is observed with drugs, or frequently with their metabolites. Experimentally, the existence of IgE antibodies against tartrazine has been demonstrated by Moneret-Vautrin et al. (98). There is no evidence at present that untoward reactions to food colours are mediated through specific IgE antibodies normally implicated in Type I allergic reactions (96).

Weliky et al. (154) found IgD antibodies specific to tartrazine in six allergic subjects. The role of these antibodies is not known. Tartrazine has also been shown to induce specific IgE antibody production in rabbits when bound to a protein carrier (67). Miller (96) states, however, that demonstrating that a tartrazine conjugate is antigenic when injected and gives rise to a normal humoral response in an animal model does not imply that it can provoke an allergic reaction.

In some metabisulfite-sensitive patients skin tests, peroral challenge tests and passive cutaneous transfer tests with metabisulfite have been reported positive, suggesting that some metabisulfite-induced reactions might be mediated by IgE (158).

A delayed type of hypersensitivity (Type IV) is possible after ingestion of additives (azo dyes, BHT, BHA, parabens, etc.), manifesting as eczema (101). Sensitization may originally develop after skin contact with the additive, e.g.,

occupational contact with foods, ointments or cosmetics.

Immunological contact urticaria (ICU) reaction is mediated by specific IgE, thus being a Type I allergic reaction. The mechanisms underlying non-immunological contact urticaria (NICU) are mostly unknown. Histamine is obviously not involved in NICU (80). The NICU reaction can be abolished with peroral aspirin, suggesting that prostaglandins are at least in part responsible for the wheal and flare reaction (82).

Pharmacological and other mechanisms

According to the results of several studies, in 8–25 % of patients with asthma or chronic perennial rhinitis the symptoms are provoked by ASA. In patients with chronic or recurrent urticaria the figure is about 20 % (55). ASA interferes with the synthesis of prostaglandins and leukotrienes. Adverse reactions to ASA may be caused by the inhibition of cyclooxygenase, which provokes inhibition of prostaglandin synthesis, particularly PGE. It acts normally as a bronchodilator.

It is possible that some food additives have the same kind of action as ASA on the cyclooxygenase pathway. This is supported by the observation that many patients who are intolerant to ASA also experience adverse reactions to tartrazine, other dyes and benzoates. However, tartrazine has not been observed to inhibit the prostaglandin pathways (47). There is some evidence that leukotrienes (13), bradykinin (106), and leucocyte inhibition factor (151) may be involved in adverse reactions to food additives.

Augustine & Levitan (8) have observed that some *colouring agents*, xanthines and erythrosin, alter the membrane permeability of neurons in animal studies. They suggested that this action may explain the behavioural disorders which have been attributed to colorants.

Sodium nitrite is used as an antioxidant and antimicrobial agent in various foodstuffs, e.g., cooked pork meats. The authorized and widely accepted daily intake is 0.2 mg/kg. Daily consumption commonly exceeds this figure, par-

ticularly in children. Moneret-Vautrin et al. (99) have shown that an oral challenge test with 30 mg sodium nitrite may cause urticaria, intestinal disorders or headache. This has been confirmed, e.g., by Henderson & Raskin (62). The mechanism by which sodium nitrite acts is unclear. It may cause cellular anoxia and inhibit the protective enzymatic activities of the intestinal mucosa. This may lead to increased permeability of the mucosa to allergens. In addition, sodium nitrite may in some way enhance the effect of histamine present in many foods.

Intolerance to *wines* is fairly common. Usually, only small quantities of a certain wine are enough to induce adverse effects: flush, tachycardia, palpitations, rhinitis or asthma, and skin symptoms (14). The reactions are not immunologically mediated. Moneret-Vautrin (101) has suggested several mechanisms as an explanation:

- the histamine-releasing action of ethanal (aldehyde)
- richness of histamine in certain red or white wines
- intolerance to benzoates, which are present in great quantities in certain grapes
- intolerance to quinine, present in many aperitifs
- intolerance to some preservatives, such as sulfur dioxide.

Harada et al. (60) showed that vasomotor and cardiac problems arise particularly in subjects who have hepatic aldehyde dehydrogenase deficiencies, in association with a raised level of blood acetaldehyde.

Acute urticaria attacks provoked by alcohol itself have been occasionally observed (70, 109).

Sulfur dioxide, sodium and potassium bisulfite and metabisulfites are widely used for the preparation, processing and storage of foods (131). Sodium and potassium bisulfite and metabisulfites are converted into sulfurous acid in solutions, and sulfur dioxide itself. A restaurant meal can contain up to 100 mg of sulfites (137), and 100 ppm of sulfur dioxide can be found in soft drinks (44).

The mechanisms by which sulfur dioxide produces symptoms mimicking allergy are open to speculation. Asthmatic symptoms 1-2 min after ingestion of soft drinks may be due to inhalation of gas, or rapid absorption across the buccal mucosa (44). Inhalation of sulfur dioxide at 1 ppm may cause bronchoconstriction in asthmatics (74-76). Ingestion of encapsulated potassium metabisulfite also produces severe systemic symptoms in some sensitive asthmatic patients (76, 137). This may be due to deficiency of a reactive sulfite oxidase in sulfite-sensitive asthmatics (66). Delohery et al. (31) suggested that ingested metabisulfite

Table 1
Symptoms and signs in the skin caused by food additives

Symptoms and signs	Mechanism(s) underlying the reaction
Acute urticaria	Type I allergy (IgE-mediated)
Exacerbation of chronic and recurrent urticaria	Type III allergy (immunocomplex disease)
Angioedema	Intolerance
Contact urticaria	
- immunological (ICU)	Type I allergy (IgE-mediated)
- non-immunological (NICU)	Mechanism(s) unknown
Purpura	Thrombocytopenia (Type II reaction)
	Allergic vasculitis (Type III reaction)
	Unknown (non-thrombocytopenic purpura)
Fixed and lichenoid eruptions	Type IV allergy?
Primary irritant dermatitis	Irritancy
Allergic contact dermatitis	Contact allergy (Type IV)
Photodermatitis	Photoallergic or phototoxic

may initiate an orobronchial reflex or variable inhalation of SO₂ during swallowing.

REACTIONS IN THE SKIN

The most important skin symptoms are listed in Table 1. In addition to these, exanthematous rashes mimicking virus exanthemas are often suspected to be caused by foods and food additives. Such reactions will not be discussed in detail because they are difficult to distinguish from exanthemas due to several other causes.

Urticaria and angioneurotic edema

Chronic and recurrent urticaria from ingested food additives has gained more attention than other possible side effects from these chemicals (Table 2).

The provocative effect of ASA in urticaria was realized in the late fifties (20, 148). It was soon found that this phenomenon was not restricted to ASA but that other salicylates were also capable of exacerbating urticaria (102). Later, all the newly introduced inhibitors of the cyclooxygenase pathway of arachidonic acid metabolism (indomethacin, ibuprofen, naproxen, diclofenac, etc.) have been found to worsen urticarial symptoms.

Since 1959 azo dyes, particularly tartrazine, new coccine, and sunset yellow, have been known to be precipitating factors in chronic urticaria (33, 45, 69, 88). Urticarial reactions from azo dyes, benzoic acid and other common food additives have been found in ASA-sensitive patients more often than in patients non-

reactive to ASA and other inhibitors of prostaglandin synthesis (23, 69, 94, 123). Because of the frequent harmful reactions (urticaria and asthma) azo dyes have been removed from most foodstuffs and medicines in many Western countries.

In alcoholic beverages there are several agents which can cause urticaria and angioneurotic edema, e.g., salicylates, flavouring substances, and ethanol itself (39, 63, 70, 89, 109). The mechanism of ethanol urticaria is unclear. In the case of Ormerod & Holt (109), neither H1 nor H1 + H2 antihistamines prevented whealing, but indomethacin, 25 mg qds, Naloxone infusion, 0.4 mg/min, and sodium cromoglycate, 100 mg qds, did.

In recent years, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), sorbic acid, canthaxanthine, quinoline yellow, nitrites and nitrates, clove, and cinnamon have been added to the list of urticaria inducers (55, 68, 150) (Table 2).

Angioneurotic edema is a common accompanying symptom in chronic and recurrent urticaria, occurring in two thirds of the patients, usually on the face (lips, eyelids, cheeks), tongue and on the hands and feet (23, 68). Other symptoms frequently reported by patients with chronic urticaria are vasomotor or intrinsic rhinitis (132), and abdominal troubles, such as aches and pain in the upper abdomen, diarrhoea, and abdominal swelling (68).

Contact urticaria appears as a wheal and flare reaction on normal or eczematous skin within some minutes to a hour after agents capable of producing this type of contact reaction have been in touch with the skin. Mild reactions show only redness and itching but no wheals. The difference between an immediate irritant (toxic) reaction and contact urticaria is far from clear and there is much confusion in using terms such as *contact urticaria*, *immediate contact reaction*, *atopic contact dermatitis*, and *protein contact dermatitis*. Immediate contact reaction includes both urticarial and other reactions, whereas protein contact dermatitis signifies allergic or non-allergic eczematous dermatitis caused by

Table 2

Food additives causing or aggravating urticaria and angioneurotic oedema

Benzoic acid, benzoates
Sorbic acid, sorbates
Azo dyes (tartrazine and others)
Canthaxanthine, beta-carotene
Annatto
Quinoline yellow
Butylhydroxytoluene (BHT), Butylhydroxyanisole (BHA)
Nitrites and nitrates
Spices (e.g. cinnamon, clove, white pepper)
Ethanol

proteins or proteinaceous materials. Dermatitis is usually seen in food handlers, veterinarians and slaughterhouse workers (65). Atopic contact dermatitis is an immediate type of allergic contact reaction in atopic people (54). It may be regarded as a special form of immunological or allergic contact urticaria.

Contact urticaria is also known as *contact urticaria syndrome* (91), which, in addition to localized urticaria and eczematous dermatitis, also includes generalized urticaria or asthmatic symptoms.

According to the mechanism underlying the urticarial reaction, contact urticaria is divided into two main types: immunological (ICU) and non-immunological contact urticaria (NICU). There are still some substances which cannot be classified as agents causing either ICU or NICU.

Immunological contact urticaria (ICU). Of the many food additives, spices are the most common causes of ICU (Table 3). Mustard, cinnamon, and cayenne produce both ICU and NICU reactions, but many other spices, such as cardamom, caraway and coriander, produce mostly ICU. Persons working in grill-bars and pizzerias are exposed to many powdered spices and may get occupational ICU dermatitis on the hands and face. The most common non-occupational ICU reactions from spices appear as cheilitis, perleche and eczema around the lips, as well as mucosal edema in the mouth ("lump" in the larynx), especially in children

(108). Systemic reactions from ingested spices are occasionally to be expected. Peppers have caused nasobronchial and gastrointestinal symptoms and shock (121), and cinnamon and clove chronic urticaria (55, 150).

Immediate allergy to various spices is usually connected with birch pollen allergy (108). There are obviously common antigenic determinants in birch pollen, various fruits, such as apples and pears, and carrot, celery tuber (53), and spices.

Cremodan SE 40®, a food consolidator containing mono-, di- and triglycerides of fatty acids, sodium alginate, polysorbate 80, guar gum, carrageenan (21), and butylhydroxytoluene (111), have been reported to be the cause of contact urticaria in a few cases.

Non-immunological contact urticaria (NICU). Of the spices, cinnamon, mustard and cayenne are the most well-known producers of NICU (Table 4). Balsam of Peru, benzoic acid and benzoates, sorbic acid and sorbates, cinnamic acid and cinnamates, and cinnamaldehyde readily produce contact urticaria when applied to the skin. The concentration capable of causing NICU depends on the vehicle, the skin region exposed, and on the mode of exposure (80, 81). Sorbic acid, for example, causes wheal and flare reactions when tested at 5% in petrolatum, but only a few people react to a 0.2% mixture.

The back skin, the face, and the extensor sides of the upper extremities react to NICU agents more readily than other parts of the body, the soles and palms being the least sensitive areas (51, 80).

NICU reactions on the hands are to be expected among employees handling food additives in the food industry. In a kindergarten, salad

Table 3

Food additives causing immunologic contact urticaria

Various spices
- cinnamon
- mustard
- cayenne
- cardamom
- caraway
- coriander, etc.
Cremodan SE 40 (di- and triglycerides)
Polysorbate 80
Sodium alginate
Guar gum
Carrageen

Table 4

Food additives producing non-immunologic contact urticaria

Benzoic acid and benzoates
Sorbic acid and sorbates
Cinnamic acid and cinnamates
Cinnamaldehyde
Various spices (cinnamon, mustard, etc.)

dressing containing benzoic acid and sorbic acid raised perioral NICU reactions when the children had fun smearing dressing around their mouths (25).

Purpura. Allergic purpura appeared 3 h after peroral provocation with 10 mg of tartrazine in a 51-year-old man suffering from cold urticaria and recurrent episodes of purpura (113). The provocation was repeated 4 times, resulting in purpura each time. Purpura with fever, malaise, and pains in the abdomen and joints in five patients (95) and allergic purpura in one patient (28) were apparently caused by tartrazine. Thrombocytopenic (10) and non-thrombocytopenic purpuras (86) from quinine are well documented.

Fixed, bullous and lichenoid eruptions. Quinine frequently produces lichenoid eruptions (3), and less frequently bullous and fixed eruptions (fixed erythema) (32).

Primary irritant contact dermatitis. The usual causes of irritant dermatitis in food handlers are wet

work and detergents. However, some food additives are possible irritants and may partly be responsible for hand dermatitis. Table 5 lists some of the irritants which bakers may encounter (43).

Allergic contact dermatitis. Parabens are important contact allergens in cosmetics and other dermatological preparations. They are also used as preservatives in food and drugs (Table 6). Although parabens occasionally cause allergic contact dermatitis among workers in the food industry, they do not seem to affect consumers, even those who are sensitized (126).

Sorbic acid has become more and more popular as a preservative in bakery products in recent years. Contact allergy is fairly infrequent and is mostly due to the use of creams containing sorbic acid. Ingested sorbic acid has not been reported to produce or worsen eczematous dermatitis.

Contact sensitivity to BHT and BHA is rare. Roed-Petersen & Hjorth (118) reported two female patients with hand dermatitis. One patient was allergic to BHT but not BHA; the other reacted to both BHA and BHT. A cook had skin trouble after handling and eating mayonnaise containing BHA (41).

Gallates in margarine and peanut butter have been reported to cause occupational hand dermatitis. (15, 16, 18, 71). Ingested gallates appear to be harmless even in hypersensitive individuals.

Vitamin E (tocopherol) is a potent contact sensitizer (42). Ingested vitamin E, however, has not been reported to produce allergic reactions.

Propylene glycol (PG) is a good solvent and vehicle for many substances, in addition to which it is antimicrobial and hygroscopic (isotonic concentration about 2 % in water) (92). According to the FAO/WHO its estimated acceptable daily intake is up to 25 mg per kg body weight, i.e. 1.75 g/70 kg. Our average daily intake of PG is estimated to be about 0.5 g (4).

Peroral ingestion of 2–15 ml of PG produced an exanthematous reaction in 8 of 10 persons with a positive patch test with 2 % PG in water.

Table 5

Causes of primary irritant contact dermatitis
(especially in bakers)

Emulsifiers
Acetic, ascorbinic and lactic acids
Potassium bicarbonate
Potassium bromate and iodide
Calcium acetate and sulfate
Bleaching agents

Table 6

Food additives inducing contact allergies

Parabens
Sorbic acid
Butylhydroxytoluene and -aniso
Gallates (octyl-, lauryl-)
Vitamin E (tocopherols)
Propylene glycol
Spices, essential oils and balsams
Azo dyes
Karaya gum
Benzoyl peroxide
Ethanol

The corresponding number among those reacting to 10–100 % PG in patch testing was seven of 28 cases and none of 20 control subjects (57). In one of the patients, PG in food was the apparent cause of recurrent rashes. In another study, 15 ml of PG produced an exanthematous rash in two of five patients with a positive patch test to 2–100 % PG (5). Thus, PG is a rare but possible cause of exanthematous rash even in amounts ingested in daily food.

Many spices and other flavouring agents are potent contact allergens but the exact composition of the chemicals responsible for contact sensitization is not usually known. Eugenol, cinnamic aldehyde, cinnamic acid, and cinnamyl alcohol are well-known sensitizers present in various balsams, spices and perfumes (64, 97).

Niinimäki (107) made challenge tests with various spices (30 mg in gelatine capsules) in 71 patients with Peru balsam allergy and in 50 dermatological patients with negative patch test results. Seven of the Peru balsam allergic patients (10 %) had objective symptoms (urticaria, facial dermatitis, conjunctival irritation, and pompholyx of the hands). None of the 50 control patients had symptoms from ingested spices.

Rare causes of occupational allergic hand dermatitis in bakers are benzoyl peroxide, karaya gum, and azo dyes (43). Ethanol is also capable of producing contact allergy, and allergic patients may have an erythematous rash after drinking alcoholic beverages (29, 35).

Photodermatitis. Cyclamate is the only food additive which has been reported to cause photodermatitis via an apparently allergic mechanism (73, 83).

REACTIONS IN THE AIRWAYS

Asthma, rhinitis and nasal polyposis are the main hypersensitivity symptoms of the respiratory tract.

Azo dyes and benzoates

In the late 1950s it was discovered that food colorants provoked asthma (88, 134). Of them,

tartrazine has been the most studied and its role in asthmatic reactions was established in the 1960s (22).

Since 1919 ASA has been reported to cause serious reactions in some patients with asthma (27). The reported figure of intolerance to ASA and other non-steroidal anti-inflammatory drugs (NSAID) in patients with asthma differs widely, from 1 to 44 % (146, 152). In an unselected population an incidence of 0.5 % has been reported (125).

Patients can have had rhinitis associated with nasal polyps for many years before manifesting asthmatic intolerance to ASA. It is possible that the intolerance to ASA will extend to food additives, resulting in adverse reactions via much the same mechanism as that producing ASA intolerance. However, reactions to food additives also occur without ASA-sensitivity (120, 135). Concomitant reactivity to tartrazine has been reported in 8–50 % of ASA-sensitive asthmatic patients (123, 132, 133, 136). Similar concomitant reactivity with various benzoates has also been found (69). One explanation may be the similarity of the molecule structure (96). Many of the natural salicylates are present in food products, such as wines. Synthetic salicylates are flavouring agents in sweets, ice-cream, soft drinks, etc.

Rosenhall (120) tested 504 patients with asthma and rhinitis, 106 of whom reacted to food colorants, preservatives or analgesics. Of 33 patients who reacted to tartrazine, 42 % were also intolerant to ASA and 39 % to sodium benzoate. Stenius & Lemola (136) tested 140 asthmatics of whom 17 reacted to tartrazine. Six of the 17 subjects did not react to ASA. One third of the patients with a positive reaction to tartrazine also had a history of reactions to drinks or foods containing colorants. In an open oral challenge test, 6 % of urticaria patients, 7 % of asthma patients and 14.5 % of urticaria and asthma patients were intolerant to tartrazine (157). Intolerance to benzoate varied from 2.5 % in rhinitis to 11.5 % in asthma.

Some of the asthmatic patients experience rhinitis only when challenged with ASA, tartrazine or benzoates. There were 104 patients with chronic rhinitis in the Rosenhall study

(120); 4 % of them had a positive reaction with nasal symptoms and 16 % had a doubtful reaction when challenged.

It has been assumed that adverse reactions of the respiratory tract to food additives are less frequent in children than adults. Vedanthan et al. (146), Osterballe et al. (112) and Weber et al. (152) found only few asthmatic children who reacted to ASA, food colorants and benzoates.

Many of the studies on food colorants have been open and poorly controlled. Recently, Morales et al. (103) made a placebo-controlled study and challenged 47 asthmatic patients with intolerance to ASA. Only one patient had a respiratory reaction to tartrazine on two successive occasions. Genton et al. (46) also made a placebo-controlled study and challenged 17 asthmatics, whose case history suggested an intolerance to ASA or additives, with tartrazine and sodium benzoate. Only two patients had a mild positive reaction. Additionally, two patients reacted with urticaria.

At present it seems that adverse respiratory reactions to food colorants and benzoates are infrequent. Asthmatic patients with ASA-intolerance may have a greater risk of experiencing these reactions. If the reaction occurs, it is usually mild; life-threatening reactions are extremely rare (139, 140).

Sulfites

Prenner & Stevens (117) were the first to report on a patient who experienced an anaphylactic reaction after ingestion of sulfites in foods. Sulfur dioxide and sulfites in foods have been estimated to precipitate acute asthma in 5 to 10 % of asthmatics (93). Bronchoconstriction after oral administration of sulfur dioxide was seen in four of 17 adult asthmatics by Genton et al. (46). Towns & Mellis (144) reported that as many as 19 of 29 children with chronic asthma reacted with bronchoconstriction when challenged with metabisulfite in a solution of 0.5 % citric acid. None of the children reacted to metabisulfite in capsule form. Wolf & Nicklas (155) have described a 7-year-old child who experienced cough and chest tightness immediately after ingestion of a restaurant salad. The

reaction was confirmed in an oral challenge test. There is a significant amount of sulfur dioxide in many wines and beers. A glass of wine could have an additive effect in viral-induced bronchospasm and become clinically important (48). Sulfites in medicaments have caused bronchoconstriction in a few cases (74, 76, 128, 129, 145).

It seems that sulfites cause adverse respiratory reactions much more often than food colorants and benzoates. These reactions are obviously non-specific in nature, similar to the response to metacholine or histamine (19). Reactions to sulfite may be severe and not readily recognized if not suspected. There are only a few reports of adverse reactions to sulfites in non-asthmatics.

Other agents

"The Chinese restaurant asthma" is suggested to be caused by monosodium 1-glutamate (1, 2, 124). There are, however, studies in which double blind provocation tests have produced no asthmatic symptoms at all (49, 52, 104). Numbness of the neck, headache, facial pressure, and chest pain have also been claimed to be symptoms of the "Chinese restaurant syndrome" in some individuals (79).

Occupational asthma induced by inhalation of dust from spices, such as powdered coriander, curry and paprika, has been described (143).

REACTIONS IN OTHER ORGANS

Hypersensitivity reactions to food additives in other organs than the skin or respiratory tract are rare and poorly documented. When other symptoms are absent, the incidence of gastrointestinal manifestations associated with additives is not known. Farah et al. (37) showed convincingly that only a small number of patients with gastrointestinal symptoms have verifiable specific food intolerance; the greater number have symptoms attributable to psychogenic causes. It is more than probable that the same conclusions also apply to food additives (85, 90, 114, 115). Headaches and migraine, even joint

and muscular pains, arthralgias and arthritis have been claimed to be provoked by food allergies (121, 156), but the objective evidence is sparse.

Overreactivity, with concentration and learning difficulties, may be present in 1–5% of young children (84). Feingold (40) claimed that hyperactivity in children is associated with the ingestion of salicylates and cross-reacting food additives. He reported that 30–50% of hyperactive children in his practice had complete remission of symptoms on a salicylate and additive free diet. However, these observations have not been confirmed in double blind studies. The US National Institutes of Health (105) evaluated the evidence and concluded that it does not support the Feingold hypothesis, although it does not exclude the possibility that hyperactive behaviour could be attributable to food dyes in a minority of cases. Weiss et al. (153) observed deterioration of behaviour in two of 22 hyperactive children challenged with a mixture of food dyes after 3 months on an additive-free diet.

TESTS FOR HYPERSENSITIVITY REACTIONS

Because of the large variety of hypersensitivity and other untoward reactions to foods and food additives there is no simple all-embracing *in vivo* or *in vitro* test method to detect the cause of such reactions. In immediate (type I) allergic reactions, the allergen is usually a protein inducing IgE production; this can be shown both with *skin* and *challenge tests* as well as *in vitro* test in a laboratory

Patch tests are needed for detecting contact allergies. The tests are applied to the skin of the back or upper arm for 24–48 h, and the results are read 24–72 h after the removal of the patches. Both irritant and allergic reactions may develop (9).

Open application tests and rub tests are used in seeking the causes of contact urticarial and other immediate reactions and sometimes also in detecting delayed contact allergies. In the

open application test a small amount (approx. 0.1 ml) of test substance is applied to healthy skin on a 5 × 5 cm area of the extensor side of the upper extremity or on the back (56). Allergic (ICU) reactions are seen in 15–20 min, non-immunologic reactions in 1 h. It is also possible that, in spite of a patient history suggestive of contact urticaria, normal-looking skin is non-reactive but a positive reaction can be seen in diseased skin. Therefore, open application tests are often done on the back of the hand.

The rub test is a modification of the open application test. The test substance is gently rubbed into a skin area (usually the hands) where the reaction had been.

A positive open application test result comprises a wheal and flare reaction, but in weaker reactions only redness (80). In hands, especially in the rub test, small vesicles may be the only response, appearing within 15–30 min and disappearing within a couple of hours (65, 77).

The repeated open application test (ROAT) is done in questionable cases of delayed contact allergies when the significance of the reaction seen in patch testing is not clear (59). Approximately 0.1 of test substance is applied b.i.d. to a 5 × 5 cm area on the volar aspect of the forearm, on the cubital fossa, on the outer aspect of the upper arm, or on the back. In positive cases, eczematous dermatitis appears on the test area, usually on the second to the fifth day. If no sign of dermatitis is seen in a week, the test is discontinued and the result is considered negative.

The use test. The product suspected responsible for the reaction is used as usual and the skin response is followed for up to 1 month. Both weak allergens and primary irritant substances may produce reactions in the use test.

Oral challenge tests

Oral mucosal test. The simplest way to assess the role of spices and other substances suspected of producing reactions in the mouth and adjacent areas is to spread the substances on the oral

mucosa (108). Within 15–20 min, swelling of the oral mucosa, lips or throat, an attack of allergic rhinitis and/or conjunctivitis may appear. In rare cases, a systemic reaction (urticaria) may occur.

Peroral challenge test. The substance to be tested is given to the patient in non-transparent gelatine capsules preferably in a double blind manner. The dose should be about the average daily dose used by the population. In some cases, individual doses are needed.

In cases of urticaria, possible reactions are followed up to 24 h, although the reaction is usually seen within 1–4 h. In patients with purpura and in those with suspected internal exacerbation of contact dermatitis, a longer exposure and follow-up time (up to several days) may be needed.

Subjective sensations are always regarded as negative challenge test results. Only clear-cut reactions are to be regarded as positive results. In chronic and recurrent urticaria, a marked worsening of urticaria with or without angio-neurotic edema is suggestive of a true hypersensitivity reaction. In cases of purpura, widespread purpurial patches, and in cases of internal exacerbation of contact dermatitis, eczema and/or pompholyx reactions are significant. The assessment of respiratory symptoms must also be based on objective criteria. In rhinitis, the number of sneezes are counted, the mucus flow from the nose measured and handkerchiefs used counted. Nasal obstruction is usually measured by a peak flow meter (nasal peak expiratory flow) or a rhinomanometer. The asthmatic response is expressed as change in PEF (peak expiratory flow) or FEV₁ (forced expiratory volume in 1 s). A drop of 20% is regarded as significant. The respiratory reaction may be delayed up to 8 h. All equivocal and positive challenge tests should be repeated.

The importance of the double blind challenge test technique was clearly demonstrated in a study by Hannuksela & Lahti (58). Peroral challenge tests with common food additives were made in 44 patients with chronic urticaria, in 91 patients with atopic dermatitis, and in 123 patients with non-atopic eczematous dermatitis

as a control group. Positive and equivocal reactions were seen in all groups, and there were no differences between the various additives and the placebo in their capacity to produce these reactions.

In vitro test

Very few untoward reactions to food additives other than spices are mediated by IgE and therefore, as yet, there are no commercial RASTs for food additives available.

The basophil degranulation test for immediate allergy and lymphocyte transformation test might well be worth trying in cases of food additive sensitivity (11). Cytotoxic test has been used in food allergy (12), but is difficult to reproduce and unreliable (130), and the interindividual results may vary grossly from time to time (122).

Summarizing, at present a controlled peroral challenge is the only reliable means of testing systemic reactions to food additives. Skin tests are irreplaceable in the diagnosis of many skin reactions.

TREATMENT

Avoidance diets

Dietary restrictions have been widely used as a diagnostic and therapeutic tool in chronic and recurrent urticaria. Good or excellent results have been reported in 31–81% of the patients in these experiments (50, 72, 87, 94, 119, 147, 149). August (7) successfully treated 22 urticaria patients, sensitive to tartrazine and sodium benzoate, with disodium cromoglycate (DSCG) and an exclusion diet. A diet free from NSAIDs and food additives had a favourable effect in six of nine asthmatics and in 14 of 15 patients with urticaria (46). The studies mentioned above were, however, all uncontrolled and therefore the results are open to doubt.

The duration of the sensitivity to food additives, whether permanent or temporary, has never been evaluated. For ASA-intolerance it is known that once it has developed it lasts for years, and caution for an indefinite period is advocated.

Over 10 years ago, a temporary refractory state was found to follow intake of ASA in ASA-induced asthma (159). Since then, this type of induced tolerance, and treatment of asthma with low-dose ASA regimens has been used with some success (24, 138), but long-term ASA treatment seems to be less effective in severe corticosteroid-dependent, ASA-sensitive asthmatics (34). In chronic asthma, the avoidance of tartrazine and benzoates has been found of no use (141).

Five of six patients with ASA-provoked urticaria became tolerant to ASA after a single dose of 30–515 mg of ASA (6). These five patients remained free of symptoms during the following weeks when taking 650 mg of ASA daily. We have succeeded in desensitizing some asthma patients with ASA-sensitivity, but our experience with urticaria has been disappointing.

Treatment with drugs.

Ortolani et al. (110) showed that premedication with 800 mg oral DSCG protects against the effects of challenge with ASA and tartrazine in patients with urticaria. They also reported that 8 weeks' treatment with DSCG ameliorates symptoms caused by foods and additives, compared to placebo. Conflicting results have also been published (61, 142). Oral DSCG has been found to prevent asthmatic reaction to metabisulfite (127). Dahl (30) reported that oral DSCG protected against an asthmatic reaction to foods, but neither oral nor inhaled DSCG protected the patient against bronchospasm caused by ASA. Oral DSCG is poorly absorbed and it is suggested that the activity occurs within the gastrointestinal mucosa, and DSCG modifies the way in which food allergens are transferred and metabolized in the gut.

In ICU, peroral antihistamines are effective, and in very rare cases systemic corticosteroids may be needed. NICU reactions are mild and no treatment is needed. Avoidance of causative agent(s) is sufficient.

ASA and other inhibitors of prostaglandin synthesis have been found to prevent diarrhoea due to food intolerance (17).

Patients with irritant and allergic contact dermatitis are treated with corticosteroid creams and ointments when necessary.

In summary, in cases of food additive intolerance a diet and/or oral DSCG may be worth trying, especially in sulfite-sensitive persons and in certain cases of ASA-intolerance. It is also possible that daily low-dose intake of natural salicylates, benzoates and other food additives might even be beneficial, analogically to low-dose ASA in ASA-sensitive patients.

REFERENCES

1. Allen, D. H. & Baker, G. J.: Chinese-restaurant asthma. *N. Engl. J. Med.* 305, 1154–1155, 1981.
2. Allen, D. H., Delohery, J., Baker, G. J. & Wood, R.: Monosodium glutamate-induced asthma. *J. Allergy Clin. Immunol.* 71, 98, 1983.
3. Almeyda, J. & Levantine, A.: Drug reactions XVI. Lichenoid drug eruptions. *Br. J. Dermatol.* 85, 604–607, 1971.
4. Andersen, K. E.: Vissa bieffekter av konserveringsmedel och emulgatorer. *Sv. Farm. Tidskr.* 87, 32–34, 1983.
5. Andersen, K. E. & Storrs, F. J.: Hautreizungen durch Propylenglykol. *Hautarzt* 33, 12–14, 1982.
6. Asad, S. I., Youlten, L. J. F. & Lessof, M. H.: Specific desensitization in "aspirin-sensitive" urticaria; plasma prostaglandin levels and clinical manifestations. *Clin. Allergy* 13, 459–466, 1983.
7. August, P. J.: Successful treatment of urticaria due to food additives with sodium cromoglycate and an exclusion diet. In Pepys, J. & Edwards A. M. (eds.): *The mast cell: its role in health and disease*, p. 584. Pitman Medical, Bath, 1979.
8. Augustine, G. J. Jr. & Levitan, H.: Neurotransmitter release from a vertebrate neuromuscular synapse affected by a food dye. *Science* 207, 1489–1490, 1980.
9. Bandmann, H.-J. & Fregert, S.: *Epicutantestung*. 2nd ed. Springer-Verlag, Berlin-Heidelberg-New York, 1982.
10. Belkin, G. A.: Cocktail purpura. An unusual case of quinine sensitivity. *Ann. Intern. Med.* 66, 583–586, 1967.
11. Benveniste, J.: The human basophil degranulation test as an *in vitro* method for the diagnosis of allergies. *Clin. Allergy* 11, 1–11, 1981.
12. Black, A. P.: A new diagnostic method in allergic disease. *Pediatrics* 17, 716–723, 1956.
13. Borgeat, P.: Leukotrienes: a major step in the understanding of immediate hypersensitivity reactions. *J. Med. Chem.* 24, 121–126, 1981.
14. Breslin, A. B. X., Hendrick, D. J. & Pepys, J.: Effect of disodium cromoglycate on asthmatic reactions to al-

- holic beverages. *Clin. Allergy* 3, 71-82, 1973.
15. Brun, R.: Kontaktekzem auf Laurylgallat und p-Hydroxybenzoës äureester. *Berufsdermatosen* 12, 281-284, 1964.
 16. Brun, R.: Eczema de contact a un antioxydant de la margarine (gallate) et changement de metier. *Dermatologica* 140, 390-394, 1970.
 17. Buisseret, P. D., Youlten, L. J. F., Heinzelmann, D. I. & Lessof, M. V. H.: Prostaglandin-synthesis inhibitors in prophylaxis of food intolerance. *Lancet* 1, 906-908, 1978.
 18. Burckhardt, W. & Fierz, U.: Antioxydantien in der Margarine als Ursache von Gewerbeekzemen. *Dermatologica* 129, 431-432, 1964.
 19. Bush, R. K., Taylor, S. L. & Busse, W. W.: A critical evaluation of clinical trials in reaction to sulfites. *J. Allergy Clin. Immunol.* 78 191-202, 1986.
 20. Calnan, C. D.: Release of histamine in urticaria pigmentosa. *Lancet* 1, 996, 1957.
 21. Camarasa, J. M. G.: Acute contact urticaria. *Contact Dermatitis* 8, 347-348, 1982.
 22. Chafee, F. H. & Settupane, G. A.: Asthma caused by FD & C approved dyes. *J. Allergy* 40, 65-72, 1967.
 23. Champion, R. H., Roberts, S. O. B., Carpenter, R. G. & Roger, J. H.: Urticaria and angio-oedema. A review of 554 patients. *Br. J. Dermatol.* 81, 588-597, 1969.
 24. Chiu, J. T.: Improvement of aspirin sensitive asthmatics after rapid desensitization and aspirin maintenance treatment. *J. Allergy Clin. Immunol.* 71, 560-567, 1983.
 25. Clemmensen, O. & Hjorth, N.: Perioral contact urticaria from sorbic acid and benzoic acid in a salad dressing. *Contact Dermatitis* 8, 1-6, 1982.
 26. Commission of the European Communities: Report of a working group on adverse reactions to ingested additives, 1981.
 27. Cooke, R. A.: Allergy in drug idiosyncrasy. *J. Am. Med. Assoc.* 73, 759-760, 1919.
 28. Criepp, L. H.: Allergic vascular purpura. *J. Allergy Clin. Immunol.* 48, 7-12, 1971.
 29. Cronin, E.: Contact dermatitis, pp. 805-806. Churchill Livingstone, Edinburgh, 1980.
 30. Dahl, R.: Oral inhaled sodium cromoglycate in challenge test with food allergens or acetylsalicylic acid. *Allergy* 36, 161-165, 1981.
 31. Delohery, J., Simmal, R., Castel, W. D. & Allen, D. H.: The relationship of inhaled sulfur dioxide reactivity to ingested metasulfite sensitivity in patients with asthma. *Am. Rev. Respir. Dis.* 130, 1027-1032, 1984.
 32. Derbeš, V. J.: The fixed eruption. *J. Am. Med. Assoc.* 190, 765-766, 1964.
 33. Desmond, R. E. & Trautlein, J. J.: Tartrazine anaphylaxis: a case report. *Ann. Allergy* 46, 81-82, 1981.
 34. Dor, P. J., Vervloet, D., Baldocchi, G. & Charpin, J.: Aspirin intolerance and asthmal induction of a tolerance and long-term monitoring. *Clin. Allergy* 15, 37-42, 1985.
 35. Drevets, C. C. & Seeböhm, P. M.: Dermatitis from alcohol. *J. Allergy* 32, 277-282, 1961.
 36. Eriksson, N. E.: Food sensitivity reported by patients with asthma and hay fever. *Allergy* 33, 189-196, 1978.
 37. Farah, D. A., Calder, I., Banson, L. & Mackenzie, J. F.: Specific food intolerance: its place as a cause of gastrointestinal symptoms. *Gut* 26, 164-168, 1985.
 38. Farr, R. S., Spector, S. L. & Wangaard, C. H.: Evaluation of aspirin and tartrazine idiosyncrasy. *J. Allergy Clin. Immunol.* 64, 667-675, 1979.
 39. Feingold, B. F.: Recognition of food additives as a cause of symptoms of allergy. *Ann. Allergy* 26, 309-313, 1968.
 40. Feingold, B. F.: Food additives and child development. *Hosp. Pract.* 8, 11-12, 1973.
 41. Fisher, A. A.: Contact dermatitis due to food additives. *Cutis* 16, 961-966, 1975.
 42. Fisher, A. A.: Reactions to antioxidants in cosmetics and foods. *Cutis* 17, 21-28, 1976.
 43. Fisher, A. A.: Hand dermatitis - A "Baker's Dozen". *Cutis* 29, 214-221, 1982.
 44. Freedman, B. J.: Asthma induced by sulphur dioxide, benzoate and tartrazine contained in orange drinks. *Clin. Allergy* 7, 407-415, 1977.
 45. Freedman, B. J.: A dietary free from additives in the management of allergic disease. *Clin. Allergy* 7, 417-421, 1977.
 46. Genton, C., Frei, P. C. & Pecoud, A.: Value of oral provocation tests to aspirin and food additives in the routine investigation of asthma and chronic urticaria. *J. Allergy Clin. Immunol.* 76, 40-45, 1985.
 47. Gerber, J. C., Payne, N. A., Oelz, O., Nies, A. S. & Oales, J. A.: Tartrazine and the prostaglandin system. *J. Allergy Clin. Immunol.* 63, 289-294, 1979.
 48. Gershwin, M. E., Ough, C., Bock, A., Fletcher, M. P., Nagy, S. M. & Tuft, D. S.: Adverse reactions to wine. *J. Allergy Clin. Immunol.* 75, 411-420, 1985.
 49. Ghezzi, P., Salmona, M., Recchia, M., Dagmino, G. & Grattini, S.: Monosodium glutamate kinetic studies in human volunteers. *Toxicol. Lett.* 5, 417-421, 1980.
 50. Gibson, A. & Clancy, R.: Management of chronic idiopathic urticaria by the identification and exclusion of dietary factors. *Clin. Allergy* 10, 699-704, 1980.
 51. Gollhausen, R. & Kligman, A. M.: Human assay for identifying substances which induce non-allergic contact urticaria: the NICU-test. *Contact Dermatitis* 13, 98-106, 1985.
 52. Grattini, S.: Chinese-restaurant asthma (letter). *N. Engl. J. Med.* 306, 1181, 1982.
 53. Halmeppuro, L. & Löwenstein, H.: Immunological investigation of possible structural similarities between pollen antigens and antigens in apple, carrot and celery tuber. *Allergy* 40, 264-272, 1985.
 54. Hannuksela, M.: Atopic contact dermatitis. *Contact Dermatitis* 6, 30-32, 1980.
 55. Hannuksela, M.: Food allergy and skin diseases. *Ann. Allergy* 51, 269-272, 1983.
 56. Hannuksela, M.: Contact urticaria from foods. In Roe, D. (ed.): contemporary issues in clinical nutrition. Nutrition and the skin, pp. 153-162. Alan R. Liss, New York, 1985.
 57. Hannuksela, M. & Förström, L.: Reactions to peroral propylene glycol. *Contact Dermatitis* 4, 41-45, 1978.
 58. Hannuksela, M. Lahti, A.: Peroral challenge tests with food additives in urticaria and atopic dermatitis. *Int. J. Dermatol.* 25, 178-180, 1986.

59. Hannuksela, M. & Salo, H.: The repeated open application test (ROAT). *Contact Dermatitis* 14, 221-227, 1986.
60. Harada, S., Agarwal, D. P. & Goedde, H. W.: Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol. *Lancet* 2, 982, 1981.
61. Harries, M. G., Oprien, I. M., Burge, P. S. & Pepys, J.: Effects of orally administered sodium cromoglycate in asthma and urticaria due to foods. *Clin. Allergy* 8, 423-427, 1978.
62. Henderson, W. R. & Raskin, N. H.: "Hot-dog" headache: individual susceptibility to nitrite. *Lancet* 2, 1162-1163, 1972.
63. Hicks, R.: Ethanol, a possible allergen. *Ann. Allergy* 26, 641-643, 1968.
64. Hjorth, N.: Eczematous allergy to balsams, allied perfumes and flavouring agents. Munksgaard, Copenhagen, 1961.
65. Hjorth, N. & Roed-Petersen, J.: Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 2, 28-42, 1976.
65. Jacobsen, D. W., Simon, R. A. & Singh, M.: Sulfite oxidase deficiency and cobalamin protection in sulfite-sensitive asthmatics (SSA). *J. Allergy Clin. Immunol.* 73, 135, 1984.
67. Johnson, H. M., Peeler, J. T. & Smith, B. D.: Tartrazine-quantitative passive hemagglutination studies on a food-borne allergen of small molecular weight. *Immunochimistry* 8, 281-287, 1971.
68. Juhlin, L.: Recurrent urticaria: clinical investigation of 330 patients. *Br. J. Dermatol.* 104, 369-381, 1981.
69. Juhlin, L., Michaelsson, G. & Zetterström, O.: Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *J. Allergy Clin. Immunol.* 50, 92-98, 1972.
70. Karvonen, J. & Hannuksela, M.: Urticaria from alcoholic beverages. *Acta Allergol. (Copenhagen)* 31, 167-170, 1976.
71. Ketel, W. G. van: Dermatitis from octyl gallate in peanut butter. *Contact Dermatitis* 4, 60-61, 1978.
72. Kirchhof, B., Haustein, U.-F. & Rytter, M.: Azetylsalizylsäure-Additiva-Intoleranzphänomen bei chronisch rezidivierender Urtikaria. *Dermatol. Monatsschr.* 168, 513-519, 1982.
73. Korbori, T. & Araki, H.: Photoallergy in dermatology. *J. Asthma Res.* 3, 213-215, 1966.
74. Koenig, J. Q., Pierson, W. E. & Frank, R.: Acute effects of inhaled SO₂ plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. *Environ. Res.* 22, 145-153, 1980.
75. Koepke, J. W., Standenmayer, H. & Selner, J. C.: Inhaled metabisulfite sensitivity. *Ann. Allergy* 54, 213-215, 1985.
76. Koepke, J. W., Christopher, K. L., Chai, H. & Selner, J. C.: Dose-dependent bronchospasm from sulfites in isoetharine. *J. Am. Med. Assoc.* 251, 2982-2984, 1984.
77. Köpman, A. & Hannuksela, M.: Contact urticaria to rubber. *Duodecim* 99, 221-224, 1983.
78. Krogh, G. von & Maibach, H. I.: The contact urticaria syndrome - 1982. *Sem. Dermatol.* 1, 59-66, 1982.
79. Kwok, R. H. M.: Chinese-restaurant syndrome. *N. Engl. J. Med.* 278, 796, 1968.
80. Lahti, A.: Non-immunologic contact urticaria. *Acta Derm. Venereol. (Stockh.)* 60, Suppl 91, 1980.
81. Lahti, A. & Maibach, H. I.: Long refractory period after one application of nonimmunologic contact urticaria agents to guinea pig ear. *J. Am. Acad. Dermatol.* 13, 585-589, 1985.
82. Lahti, A., Väänänen, A. Hannuksela, M.: Acetylsalicylic acid inhibits nonimmunologic contact urticaria. Abstract No. 12 in Abstract Book of 8th International Symposium on Contact Dermatitis, Cambridge, 20-22 March, 1986.
83. Lamberg, S. I.: A new photosensitizer. The artificial sweetener cyclamate. *J. Am. Med. Assoc.* 201, 747-750, 1967.
84. Lambert, N. M., Sandoval, J. H. & Sassone, D. M.: Prevalence estimates of hypersensitivity in school children. *Pediatr. Ann.* 7, 330-338, 1978.
85. Lessof, M. H.: Food intolerance and allergy - a review. *Q. J. Med.* 52, 111-119, 1983.
86. Levantine, A. L. & Almeyda, J.: Cutaneous reactions to food and drug additives. *Br. J. Dermatol.* 91, 359-362, 1974.
87. Lindemayr, H. & Schmidt, J.: Additivaintoleranz bei chronischer Urtikaria. *Wien. Klin. Wochenschr.* 91, 817-822, 1979.
88. Lockey, S. D.: Allergic reactions due to F D & C yellow No. 5 tartrazine, an aniline dye used as a coloring and identifying agent in various steroids. *Ann. Allergy* 17, 719-721, 1959.
89. Lockey, S. D.: Reactions to hidden agents in foods, beverages and drugs. *Ann. Allergy* 29, 461-466, 1971.
90. Lum, L. C.: Hyperventilation and pseudo-allergic reactions. PAR. Pseudo-allergic reactions. Involvement of Drugs and Chemicals 4, 106-119, Karger, Basel, 1985.
91. Maibach, H. I. & Johnson, H. L.: Contact urticaria syndrome. *Arch. Dermatol.* 111, 726-730, 1975.
92. Martindale: Propylene glycol. In Reynolds, J. E. F. & Prasad, A. B. (eds.): The extra pharmacopoeia, 28th ed., pp. 708-709. The Pharmaceutical Press, London, 1982.
93. Mathison, D. A., Stevenson, D. D. & Simon, R. A.: Precipitating factors in asthma. Aspirin, sulfites and other drugs and chemicals. *Chest Suppl.* 87/1, 50-54, 1985.
94. Michaëlsson, G. & Juhlin, L.: Urticaria induced by preservatives and dye additives in food and drugs. *Br. J. Dermatol.* 88, 525-532, 1973.
95. Michaëlsson, G., Pettersson, L. & Juhlin, L.: Purpura caused by food and drug additives. *Arch. Dermatol.* 109, 49-52, 1974.
96. Miller, K.: Allergies and idiosyncratic responses. In Walker, G. (ed.): Food toxicology. Real and imaginary problem. Taylor S. Francis, London, 1985.
97. Mitchell, J. C., Calnan, C. D., Clendenning, W. E. et al.: Patch testing with some components of balsam of Peru. *Contact Dermatitis* 2, 57-58, 1976.
98. Moneret-Vautrin, D. A., Demange, G., Selve, C., Grilliat, J. P. & Savinet, H.: Induction d'une hypersen-

- sibilite reaginique a la Tartrazine chez le lapin immunisation par voie digestive par le conjugué covalent Tartrazine-Seralbumine humaine. *Ann. Immunol. Inst. Pasteur* 130c, 419-430, 1979.
99. Moneret-Vautrin, D. A., Einhorn, C. & Tisserand, J.: Le rôle du nitrite de sodium dans les urticaires histaminiques d'origine alimentaire. *Ann. Nutr. Aliment.* 34, 1125-1132, 1980.
 100. Moneret-Vautrin, D. A., Grilliat, J. P. & Demange, G.: Allergie et intolerance a la tartrazine, colorant alimentaire et medicamenteux a propose de 2 observations. *Med. Nutr.* 16, 171-174, 1980.
 101. Moneret-Vautrin, D. A.: False food allergies: Non-specific reactions to foodstuffs. In Lessof, M. H. (ed.): *Clinical reactions to food*, pp. 135-153. John Wiley & Sons, Chichester, 1983.
 102. Moore-Robinson, M. & Warin, R. P.: Effect of salicylates in urticaria. *Br. Med. J.* 4, 262-264, 1967.
 103. Morales, M. C., Basomba, A., Delaez, A., Villamanzo, I. G. & Campos, A.: Challenge test with tartrazine in patients with asthma associated with intolerance to analgesics (ASA-triad). *Clin. Allergy* 15, 55-59, 1985.
 104. Morselli, P. L. & Grattini, S.: Monosodium glutamate and the Chinese restaurant syndrome. *Nature* 227, 611-612, 1970.
 105. National Institutes of Health Consensus Development Conference Statement: Definite diets and childhood hyperactivity. *Am. J. Clin. Nutr.* 37, 161-172, 1983.
 106. Neuman, I., Elian, R., Nahum, H., Shaked, P. & Creter, D.: The danger of yellow dyes (tartrazine) to allergic subjects. *Clin. Allergy* 8, 65-68, 1978.
 107. Niinimäki, A.: Delayed-type allergy to spices. *Contact Dermatitis* 11, 34-40, 1984.
 108. Niinimäki, A. & Hannuksela, M.: Immediate skin test reactions to spices. *Allergy* 36, 487-493, 1981.
 109. Ormerod, A. D. & Holt, P. J. A.: Acute urticaria due to alcohol. *Br. J. Dermatol.* 108, 723-724, 1983.
 110. Ortolani, C., Pastorello, E., Luraghi, M. T., Della Torre, F., Bellani, M. & Zanussi, C.: Diagnosis and intolerance to food additives. *Ann. Allergy* 53, 587-591, 1984.
 111. Osmundsen, P. E.: Contact urticaria from nickel and plastic additives (Butylhydroxytoluene, oleylamide). *Contact Dermatitis* 6, 452-454, 1980.
 112. Østerballe, O., Taudorf, E. & Haahr, J.: Asthma bronchiale af konserveringsmidler, farvestoffer og acetylsalicylsyre hos børn. *Ugeskr. Laeger* 28, 1908-1910, 1979.
 113. Parodi, G., Parodi, A. & Rebora, A.: Purpuric vasculitis due to tartrazine. *Dermatologica* 171, 62-63, 1985.
 114. Pearson, D. J., Rix, K. J. B. & Bentley, S. J.: Food allergy: How much in the mind? A clinical and psychiatric study of suspected food hypersensitivity. *Lancet* 1, 1259-1261, 1983.
 115. Pearson, D. J. & Rix, K. J. B.: Allergomimetic reactions to food and pseudo-food-allergy. *PAR. Pseudo-allergic reactions. Involvement of Drugs and Chemicals* 4, 59-105, Karger, Basel 1985.
 116. Poulsen, E.: Danish report on allergy and intolerance to food ingredients and food additives. *Toxicology forum*, Aspen Colorado, 1980.
 117. Prenner, B. M. & Stevens, J. J.: Anaphylaxis after ingestion of sodium bisulfite. *Ann. Allergy* 36, 180-182, 1976.
 118. Roed-Petersen, J. & Hjorth, N.: Contact dermatitis from antioxidants. *Br. J. Dermatol.* 94, 233-241, 1976.
 119. Ros, A.-M., Juhlin, L. & Michaelsson, G.: A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes. *Br. J. Dermatol.* 95, 19-24, 1976.
 120. Rosenhall, L.: Hypersensitivity to analgesics, preservatives and food colourants in patients with asthma or rhinitis. *Acta Univ. Ups.* 269, 1-117, 1977.
 121. Rowe, A. H. & Rowe, A. Jr.: *Food allergy. Its manifestations and control and elimination diets*. First ed. Charles C. Thomas, Springfield, 1972.
 122. Ruokonen, J.: *Secretory otitis media and allergy with special reference to food allergy and cytotoxic leukocyte test*. Thesis. Helsinki University, 1982.
 123. Samter, M. & Beers, R. F.: Intolerance to aspirin. *Clinical studies and consideration of its pathogenesis*. *Ann. Intern. Med.* 68, 975-983, 1968.
 124. Schaumburg, H., Byck, R., Gerstl, R. & Masham, J. H.: Monosodium l-glutamate: its pharmacology and role in the Chinese-restaurant syndrome. *Science* 163, 826, 1969.
 125. Schlumberger, H. D.: Drug induced pseudo-allergic syndrome as exemplified by acetyl-salicylic acid intolerance. In *Pseudo-anaphylactoid reactions*, pp. 125-203. Karger, Basel, 1980.
 126. Schorr, W. F.: The skin and chemical additives to foods. *Arch. Dermatol.* 105, 131, 1972.
 127. Schwartz, H. I.: Observations on the use of oral cromoglycate in a sulfite-sensitive asthmatic patient. *Ann. Allergy* 57, 36-37, 1986.
 128. Schwartz, H. I. & Scher, T. H.: Bisulfite intolerance manifested as bronchospasm following topical dipivefrin hydrochloride therapy for glaucoma. *Arch. Ophthalmol.* 103, 14-16, 1983.
 129. Schwartz, H. J. & Sher, T. H.: Bisulfite sensitivity manifesting as allergy to dental anesthesia. *J. Allergy Clin. Immunol.* 75, 525-527, 1985.
 130. Sethi, T. J., Lessof, M. H., Kemeny, D. M., Lambourn, E., Tobin, S. & Bradley, A.: How reliable are commercial allergy tests? *Lancet* 1, 92-94, 1987.
 131. Settignano, G. A.: Adverse reactions to sulfites in drugs and foods. *J. Am. Acad. Dermatol.* 10, 1077-1080, 1984.
 132. Settignano, G. A. & Pudupakkam, R. K.: Aspirin intolerance. III. Subtypes, familial occurrence, and cross-reactivity with tartrazine. *J. Allergy Clin. Immunol.* 56, 215-221, 1975.
 133. Spector, S. L., Wangaard, C. H. & Farr, R. S.: Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J. Allergy Clin. Immunol.* 64, 500-509, 1979.
 134. Speer, F.: *The management of childhood asthma*. Charles C. Thomas, Springfield, 1958.
 135. Speer, F., Denison, T. R. & Baptist, J. E.: Aspirin allergy. *Ann. Allergy* 46, 123-126, 1981.

136. Stenius, B. S. M. & Lemola, M.: Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clin. Allergy* 6, 119-129, 1976.
137. Stevenson, D. D. & Simon, R. A.: Sensitivity to ingested metabisulfites in asthma subjects. *J. Allergy Clin. Immunol.* 68, 26-32, 1981.
138. Stevenson, D. D., Pleskow, W. W., Gurd, J. G., Simon, R. A. & Mathison, D., A.: Desensitization to acetylsalicylic acid (ASA) in ASA-sensitive patients with asthma/rhinosinusitis. *PAR. Pseudo-allergic reactions. Involvement of Drugs and Chemicals* 3, 133-156. Karger, Basel 1982.
139. Stevenson, D. D. & Simon, R. A.: Sulfites and asthma. *J. Allergy Clin. Immunol.* 74, 469-474, 1984.
140. Stevenson, D. D., Simon, R. A., Lumry, W. R. & Mathison, D. A.: Adverse reactions to tartrazine. *J. Allergy Clin. Immunol.* 78, 182-191, 1986.
141. Tarlo, S. M. & Broder, I.: Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clin. Allergy* 12, 303-312, 1982.
142. Thormann, J., Laurberg, G. & Zachariae, H.: Oral sodium cromoglycate in chronic urticaria. *Allergy* 35, 139-141, 1980.
143. Toorenenberger, A. W. van & Dieges, P. H.: Immunoglobulin E antibodies against coriander and other spices. *J. Allergy Clin. Immunol.* 76, 477-481, 1985.
144. Towns, S. J. & Mellis, C. M.: The role of acetylsalicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics* 73, 631-637, 1984.
145. Twarog, F. J. & Leung, D. Y. M.: Anaphylaxis to a component of isoetharine (sodium bisulfite). *J. Am. Med. Assoc.* 248, 2030-2031, 1982.
146. Vedanthan, P. I., Menon, M. M., Bell, T. D. & Bergin, D.: Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. *J. Allergy Clin. Immunol.* 60, 8-13, 1977.
147. Verschave, A., Stevens, E. & Degreef, H.: Pseudo-allergen-free diet in chronic urticaria. *Dermatologica* 167, 256-259, 1983.
148. Warin, R. P.: The effect of aspirin in chronic urticaria. *Br. J. Dermatol.* 72, 350-351, 1960.
149. Warin, R. P. & Smith, R. J.: Challenge test battery in chronic urticaria. *Br. J. Dermatol.* 94, 401-406, 1976.
150. Warin, R. P. & Smith, R. J.: Chronic urticaria. Investigations with patch and challenge tests. *Contact Dermatitis* 8, 117-121, 1982.
151. Warrington, R. J., Sauder, P. J. & McPhillips, S.: Cell-mediated immune response to artificial food additives in chronic urticaria. *Clin. Allergy* 16, 527-533, 1986.
152. Weber, R. W., Hoffman, M., Raine, D. A. & Nelson, H. S.: Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J. Allergy Clin. Immunol.* 64, 32-37, 1979.
153. Weiss, B., Williams, J. H., Margen, S. et al.: Behavioural responses to artificial food colours. *Science* 207, 1487-1489, 1980.
154. Weliky, N., Heiner, D. C., Tamura, H. & Anderson, S.: Correlation of tartrazine hypersensitivity with specific serum IgD levels. *Immunol. Commun.* 8, 65-71, 1979.
155. Wolf, S. I. & Nicklas, R. A.: Sulfite sensitivity in a seven-year-old child. *Ann. Allergy* 54, 420-422, 1985.
156. Wrait, D. G., 1980: Cited in : Commission of the European Communities: Report of a working group on adverse reactions to ingested additives, 1981.
157. Wütrich, B. & Fabro, L.: Acetylsalicylic acid and food additive intolerance in urticaria, bronchial asthma and rhinopathy. *Schweiz. Med. Wochenschr.* 39, 1445-1450, 1981.
158. Yang, H. W., Purchase, E. C. R. & Rivington, R. N.: Positive skin tests and Prausnitz-Küstner reactions in metabisulfite-sensitive subjects. *J. Allergy Clin. Immunol.* 78, 443-449, 1986.
159. Zeiss, C. R. & Lockey, R. F.: Refractory period to aspirin in a patient with aspirin induced asthma. *J. Allergy Clin. Immunol.* 57, 440-448, 1976.

Address:

Matti Hannuksela, M.D.

Department of Dermatology

University of Oulu

SF-90220 Oulu

Finland

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.