

ADVERSE REACTIONS TO FOOD AND DRUG ADDITIVES

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Estimates are that 2000 to 20,000 agents are added to the food and pharmaceuticals that we consume.²⁵ These include preservatives, stabilizers, conditioners, thickeners, colorings, flavorings, sweeteners, and antioxidants. The box on the next page shows the most common food additives. In addition to the long list of chemicals found on many processed food labels, the reader should also be aware of the additives in pharmaceutical products. The contents of a single, brown, 1.25-mg conjugated estrogens (Premarin) tablet are listed in the box on page 138. Despite such enormous exposure to these food and drug agents, only a small number have been associated with hypersensitivity reactions.

For years, some investigators have suggested that a significant number of patients with asthma or chronic urticaria and angioedema have symptoms caused by the ingestion of food additives. Despite many studies that have attempted to establish the prevalence of reactions to additives in patients, the true incidence of reactions remains unknown. This is due primarily to the lack of properly controlled studies. Although many anecdotal reports exist, rigorously controlled studies are rarely found in this area of clinical investigation.

The box on page 139 shows the additives that have been reported to be most commonly associated with adverse reactions. Figure 1 illustrates the chemical structure of selected additives. A common chemical structure does not link these compounds together into a single molecular configuration. These agents will be discussed individually as they relate to urticaria and angioedema, anaphylaxis or anaphylactoid reactions, and asthma.

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Common Food Additives**Antioxidants**

BHA

BHT

Extraction solvents

Dichloromethane (methylene chloride)

Trichloroethylene (TCE)

Flavoring agents

Transanethole

Benzyl acetate

(+) carvone and (–)-carvone

Ethylmethylphenolglycidate

Food color: FD&C dyes

Tartrazine (FD&C Yellow No. 5)

Erythrosine (FD&C Red No. 3)

Indigotin (FD&C Blue No. 2)

Preservatives

Benzoates

Sulfites

Sweetening agents

Aspartame

Hydrogenated glucose syrup

Saccharin

Thickening agents

Ethyl cellulose

Karaya gum

Tragacanth gum

Miscellaneous food additives

Ammonium phosphate, monobasic (monoammonium orthophosphate)

Insoluble polyvinylpyrrolidone or polyvinyl polypyrrolidone (PVPP)

Polyvinylpyrrolidone (PVP) (Polyvidone)

Potassium bromate

L-(+) Tartaric acid, ammonium, calcium, and magnesium salts

Contents of Premarin (1.25-mg tablet)

Methylcellulose
Talc triturate
Lactose
Magnesium stearate
Polyethylene glycol 20,000
Glyceryl mono-oleate
Shellac
Calcium sulfate
Titanium dioxide
Stearic acid
Edible black ink (food grade)
Canaba wax
Cornstarch
Sucrose
Gum acacia
Talc
Sodium benzoate
Gelatin
Tween 60
Propyl paraben
FD&C Yellow No. 5
Calcium carbonate
Tricalcium phosphate
Solka floc (cellulose-type material)
Sodium acetate
Sodium chloride
Neutral steroids
Estrogens

Additives Most Commonly Associated with Adverse Reactions

FD&C Dyes

Azo dyes

- Tartrazine (FD&C Yellow No. 5)
- Ponceau (FD&C Red No. 4)
- Sunset yellow (FD&C Yellow No. 6)
- Amaranth (FD&C Red No. 5)

Non-Azo Dyes

- Brilliant blue (FD&C Blue No. 1)
- Erythrosine (FD&C Red No. 3)
- Indigotin (FD&C Blue No. 2)

Parabens and Benzoates

- Parahydroxy benzoic acid
- Methyl paraben
- Ethyl paraben
- Butyl paraben
- Sodium benzoate
- Hydroxy benzoic acid

BHA

BHT

Nitrates

Nitrites

MSG

Sulfites

Sulfur dioxide

Sodium sulfite, potassium sulfite, bisulfite, metabisulfite

GENERAL CONSIDERATIONS AND DESCRIPTIONS OF GENERAL FOOD AND DRUG ADDITIVES

Dyes

Dyes approved by the Food Dye and Coloring Act (FD&C) are coal tar derivatives, the best known of which is tartrazine (FD&C Yellow No. 5). All dyes contain aromatic rings. In addition to tartrazine, the azo dyes (containing N:N-linkages) include ponceau (FD&C Red No. 4) and sunset yellow (FD&C Yellow No. 6). Amaranth (FD&C Red No. 5) was banned from use in the United States in 1975 because of claims of carcinogenicity. Non-azo dyes include brilliant blue (FD&C Blue No. 1), erythrosine (FD&C Red No. 3), and indigotin (FD&C Blue No. 2).

Sulfites and Sulfur Dioxide

Background

In AD 79 the respiratory death of Pliny the Elder was attributed to the sulfur dioxide (SO₂)-rich gases emanating from the eruption of Mount

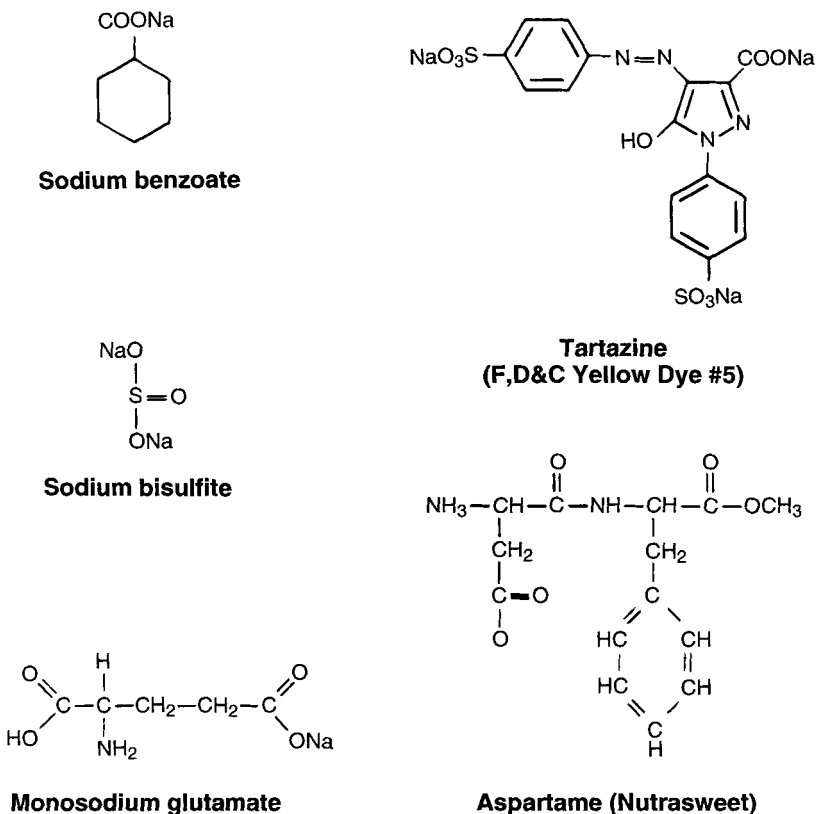


Figure 1. Chemical structures of some common food additives.

Vesuvius. Sulfur oxides, including sulfur dioxide and particulate sulfuric acid (H_2SO_4), are generated from the combustion of sulfur-containing fossil fuels and may be significant aeropollutants for asthmatic persons.^{15, 107} Plumes of exhaust fumes in the vicinity of power plants and smelters reach concentration peaks of 0.5 to 1 parts per million (ppm) of sulfur dioxide SO_2 for 5- to 10-minute intervals, yet do not exceed the National Ambient Air Quality standard of an average of 0.14 ppm for 24 hours.¹⁰

Sulfur dioxide gas inhalation challenges in asthmatic subjects induce bronchoconstriction dependent on the concentration of sulfur dioxide,^{29, 108} the minute ventilation at which it is inhaled,⁶⁵ and the severity of asthma as measured by nonspecific bronchial hyperreactivity to histamine or methacholine.¹⁰⁹ The response occurs more readily with oral than with nasal breathing¹³ and is mitigated during breathing at high-temperature, high-humidity conditions as compared with low-temperature, low-humidity conditions.⁶⁶ The maximal bronchoconstrictor response occurs over 5 to 10 minutes, and if it is not sufficient to produce

symptoms necessitating bronchodilator treatment, it does not progress over ensuing hours of continued exposure. Eucapnic hyperventilation or moderate exercise while breathing sulfur dioxide at 0.5 to 1 ppm has produced clinically significant bronchoconstriction in most asthmatics studied^{10, 12, 13, 29, 66, 67}; at 0.25 ppm, the effect is slight.¹⁴

Likewise, sulfuric acid aerosols at a concentration of 1000 $\mu\text{g}/\text{m}^3$, the threshold limit value of the Environmental Protection Agency (EPA) for occupational exposure, produce significant declines in forced expiratory volume in 1 second (FEV_1) in asthmatic subjects,¹⁴⁰ whereas aerosols at 100 $\mu\text{g}/\text{m}^3$, the "worst case scenario" for ambient exposure, do so only in asthmatic subjects during exercise.^{45, 56, 139} The prevalence of persistent cough and phlegm is significantly higher among adults living in a Utah community near a smelter, with exposure at the 100 $\mu\text{g}/\text{m}^3$ mean annual level, than among subjects in communities with exposure at one third of that level or less.²²

The effects, if any, on the induction or maintenance of bronchial hyper-reactivity of lesser concentrations of sulfur dioxide and sulfuric acid particles (for example, the annual averages in urban Southern California are in the range of 0.001 to 0.01 ppm of sulfur dioxide) singly or in combination with other aeropollutants or other factors associated with asthma such as atopic state and viral respiratory infection have not yet been clearly elucidated.

The term *sulfiting agents* is used to describe sulfur dioxide and several inorganic sulfites that may be added to foods, beverages, and pharmaceuticals. Until recently, sulfur dioxide and five sulfite salts (sodium sulfite [SO_3], sodium or potassium bisulfite [HSO_3], and sodium or potassium metabisulfite [S_2O_5]) have been listed in the code of federal regulations as generally recognized as safe (GRAS), with the provision that they not be used in foods considered to be a source of thiamine (vitamin B₁).¹

Sulfur dioxide is a nonflammable, colorless gas which readily dissolves in water and undergoes hydration to form sulfurous acid, and then dissociates to bisulfite and sulfite.⁹⁸ Under physiologic conditions at pH 7.4, sulfite is the predominant chemical species. However, in acid solution (for example, the gastric lumen with pH near 1), sulfite undergoes proton association to form bisulfite and sulfurous acid. The latter dehydrates once again to form sulfur dioxide.⁹⁸ In addition to acid pH, the generation of sulfur dioxide is also enhanced by heat (Fig. 2).

Because of this interchangeability, sulfite concentrations in food may be expressed as parts per million (ppm) of sulfur dioxide or, vice versa, sulfur dioxide content may be expressed as sulfur dioxide equivalent (SDE) or milligrams of sulfite. The conversion is parts per million of sulfur dioxide equals milligrams of sulfite per kilogram of food.

Sulfites are highly reactive and combine with a number of biologic compounds, including carbohydrates and pyridinonucleotides.⁹⁸ Sulfites also react with disulfide bonds present in proteins.²⁰ Therefore, when identifying sulfite (or sulfur dioxide) concentrations in foods, results will be expressed as free or bound sulfur dioxide. The bound sulfur dioxide

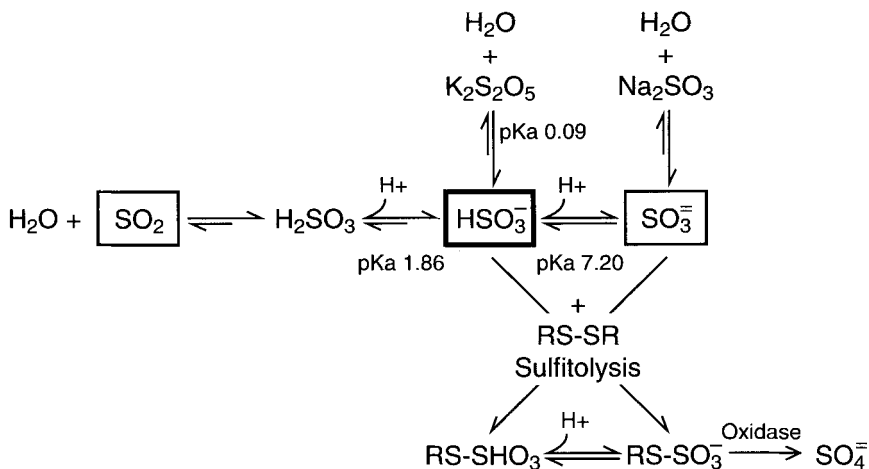


Figure 2. Equilibrium distribution of sulfur dioxide (SO_2), potassium metabisulfite ($\text{K}_2\text{S}_2\text{O}_5$), and sodium sulfite (Na_2SO_3), and interrelationships of bisulfite (HSO_3^-) and sulfite (SO_3^{2-}) with proteins (RS-SR) and sulfate (SO_4^{2-}). At physiologic pH in aqueous solution, bisulfite (HSO_3^-) dominates.

is usually reported as total sulfur dioxide, although even with the harshest of chemical extractions, all potential sulfur dioxide forms probably cannot be measured. The importance of bound sulfites causing sensitivity reactions is difficult to evaluate.

Use of Sulfites

Foods and Beverages. Sulfiting agents are still widely used in the food and beverage industry (Table 1). Sulfites can inhibit a number of enzymatic reactions, for example, polyphenoloxidase, ascorbate oxidase, lipoxygenase, and peroxidase.²⁰ Although the mechanism of action is unknown, sulfite inhibition of polyphenoloxidase is important in the control of enzymatic browning. This was the primary reason for adding sulfites to items in salad bars such as lettuce, avocados, and guacamole as well as to cut potatoes and apples, fresh mushrooms, and table grapes.^{61, 77, 86, 132} The enzyme tyrosinase, a type of polyphenol-oxidase, catalyzes tyrosine oxidation, which leads to black spot formation on shrimp. This oxidative reaction (not infection) can be prevented by sulfites.

Sulfites can also be used as inhibitors of nonenzymatic browning in wines, dried fruits, dehydrated vegetables (especially potatoes), vinegar, white grape juice, coconut, and pectin.¹³² The chemistry of these reactions is complex and beyond the scope of this chapter but has been reviewed by McWheeny et al.⁷³

The antimicrobial actions of sulfites are useful as sanitizing agents for food containers and fermentation equipment. This is due to the

Table 1. SULFITE-CONTAINING FOODS AND DRUGS

High Content	Medium Content	Low Content* (<10 ppm SO_2)
Sulfite-containing foods		
Dried fruit (excluding dark raisins and prunes)	Dried potatoes	Corn starch
Lemon juice (nonfrozen)	Wine vinegar	Hominy
Lime juice (nonfrozen)	Gravies, sauces	Frozen potatoes
Wine	Fruit topping	Maple syrup
Molasses	Maraschino cherries	Imported jam and jellies
Sauerkraut juice	<i>Pectin</i>	Fresh mushrooms
Grape juice (white; white, pink and red sparkling)	Shrimp (fresh)	Malt vinegar
	Sauerkraut	Dried cod
	Pickled peppers and cocktail onions	Canned potatoes
	Pickles and relishes	Beer
		Dry soup mix
		Soft drinks
		Instant tea
		Pizza dough (frozen)
		Pie dough
		Sugar (especially beet sugar)
		Gelatin
		Coconut
		Fresh fruit salad
		Domestic jams and jellies
		Crackers
		Cookies
		Grapes
		High-fructose corn syrup
Sulfite-preserved drugs		
Inhalants ($0.5 - 1.5$ ppm SO_2)†		Subcutaneous injections ($0.3 - 10$ ppm SO_2) Intravenous injections ($0.3 - 10$ ppm SO_2)

*Foods with low sulfite content have not been implicated in inducing reactions in sulfite-sensitive individuals.

†Rare bronchoconstriction but (?) no bronchodilation.

ability of sulfites to reduce or prevent microbial spoilage of food (for example, table grapes) and to act as selective inhibitors of undesirable organisms during fermentation.

The antioxidative effects of sulfites serve a major function in the brewing process, where oxidative changes impede development of the beer's flavor.⁸⁹ The ability of sulfites to break disulfide bonds in the gluten reaction of dough accounts for their widespread use (although in minimal residual quantities) as dough conditioners for biscuits, cookies, crackers, frozen pizza dough, and pie crusts.⁷³ In the production of maraschino cherries, sulfites are used to bleach the fruit before injecting red dye.

Pharmaceuticals. Sulfiting agents are used widely by the pharmaceutical industry as antioxidants. Some of the medications that contain

sulfites are listed in Table 2. Sulfites are also known to be present in some oral tablet formulations, but the amounts present are incapable of provoking reactions.

When compared with the concentrations of sulfite in foods, most pharmaceuticals contain small amounts of sulfite (0.25% to 1%). Unfortunately, a small amount of sulfite may produce grave consequences in rare patients when inhaled directly into the tracheobronchial tree or injected parenterally.

Sulfites are added to bronchodilator solutions of the catecholamine class to offset susceptibility of catecholamines to inactivation by oxidation.^{60, 144} Isoetharine (Bronkosol, 1 to 2 ppm of sulfur dioxide per dose), isoproterenol (Isuprel, 2.5 to 6 ppm of sulfur dioxide per dose), and the racemic epinephrine products are maintained in their reduced form by sulfite. Isoetharine routinely generates > 1 ppm of sulfur dioxide throughout the entire length of treatment with a handheld nebulizer.⁸⁹ This concentration of sulfur dioxide alone can provoke bronchospasm in non-sulfite-sensitive asthmatic patients.¹⁰⁸ Solutions of metaproterenol or albuterol do not contain sulfites, and none of the canister-type, metered-dose inhalers contains sulfites.

Regulatory Restrictions

After the discovery that some asthmatic individuals are sulfite sensitive,¹²⁶ the Food and Drug Administration (FDA), Bureau of Alcohol, Tobacco, and Firearms (BATF), and EPA moved to regulate the uses of sulfites in 1986. The FDA required the declaration of sulfites on food labels when sulfite residues exceeded 10 ppm. The BATF followed suit with wine labels. The FDA banned the use of sulfites in fresh fruits and

Table 2. PARTIAL LIST OF MEDICATIONS CONTAINING SULFITES

Type of Agent	Common Names
Bronchodilator solutions	Isoetharine (Bronkosol), isoproterenol (Isuprel)
Epinephrine	Adrenaline (all forms)
Local anesthetics	Lidocaine (Xylocaine), procaine (Novocaine)
Corticosteroids	Dexamethasone (Decadron), hydrocortisone (Hydrocortone), becamethasone (Celestone)
Antibiotics	Gentamycin (Garamycin), amikacin (Amikin), tobramycin (Nebcin)
Antiarrhythmics	Procainamide (Pronestyl), lidocaine
Analgesics	Meperidine (Demerol)
Pressors	Dopamine (Intropin), metaraminol (Aramine), norepinephrine (Levophed)
Eye drops	Pred mild, pred forte, sulfacetamide, prednisolone, dexamethasone
Solutions for total parenteral nutrition and dialysis	
Thorazine	
Others	

vegetables other than potatoes. This ban affected the practice of sulfiting lettuce, cut fruits, guacamole, mushrooms, and many other foods as well as the once common practice of sulfiting fresh fruits and vegetables in salad bars. The FDA also moved to ban sulfites from fresh, prepeeled potatoes. The EPA required that imported table grapes be detained at their port of entry until sulfite residues could no longer be detected. The FDA also enacted a regulation specifying the allowable residue levels for sulfites in shrimp. Foods that currently contain sulfites are listed in Table 1. Foods with low levels of sulfites contain ≤ 10 ppm sulfur dioxide and have not been associated with producing reactions in sulfite-sensitive subjects.

Mechanisms of Sulfite Sensitivity

The mechanisms of sensitivity reactions to sulfiting agents are unknown. Depending on the route of exposure, a number of mechanisms have been postulated. It is known that asthmatic subjects, upon inhalation of < 1 ppm of sulfur dioxide, develop bronchoconstriction.¹⁶ Fine et al²⁹ demonstrated that bronchoconstriction developed in asthmatic subjects who inhaled sulfur dioxide and bisulfite (HSO_3^-) but not sulfite (SO_3^{2-}). Alteration of airway pH was not a cause of bronchoconstriction. Thus, depending upon the pH and ionic species, asthmatic individuals develop bronchoconstriction after exposure to certain forms of sulfite. It is also recognized that some asthmatic subjects respond to either oral or inhalation challenge with sulfite, but that inhalation is more apt to induce bronchoconstriction.¹⁰² Variability in the response to sulfites in capsule and acidic solutions, administered via the oral route, has also been observed.⁶⁴ The same individuals may not always develop bronchoconstriction when challenged on repeated occasions with sulfites. The following represent further attempts to understand more fully the variables and reasons for this inconsistent response.

Inhalation During Swallowing. Delohery et al studied 10 sulfite-sensitive asthmatic subjects.²⁶ All subjects reacted to a challenge with acidic metabisulfite solution when it was administered as a mouthwash or swallowed but not when it was instilled through a nasogastric tube. Furthermore, these same individuals did not respond with changes in pulmonary function when they held their breath while swallowing the solution. Ten non-sulfite-sensitive asthmatic subjects did not react to sulfites when they were administered as a mouthwash or swallowing challenge. Researchers therefore hypothesized that some individuals respond to sulfites during oral challenges due to inhalation of sulfur dioxide during the swallowing process.

Linkage of Sulfite Sensitivity with Airway Hyperreactivity. Asthmatic persons are known to respond to various stimuli (airway irritants) at concentrations lower than those affecting normal individuals (that is, asthmatic individuals have airway hyperresponsiveness). Therefore, attempts have been made to link sulfite sensitivity with airway responsiveness as measured during histamine and methacholine inhalation

challenges. Australian investigators were unable to demonstrate a relationship between the degree of airway responsiveness to inhaled histamine and the presence of sulfite sensitivity.²⁶ Taylor et al attempted to induce sulfite sensitivity in a group of 16 asthmatic subjects.¹³³ They first established the provocative dose of methacholine producing a 20% decrease in FEV₁ (PD₂₀). The researchers next used a sulfite bronchial and oral challenge using an acidic sulfite solution to determine the presence of sulfite sensitivity; 3 of the 16 subjects reacted to the sulfiting agent with a 20% decrease in FEV₁. One week later, the patients underwent bronchial challenge with an antigen to which they were known to be sensitive. They returned 24 hours later for a repeat methacholine challenge. This was followed 24 hours later by a second sulfite challenge. After antigen challenge, only 1 additional subject showed a response to the sulfiting agent that had not been present before the antigen challenge, and there was no significant increase in airway response to methacholine. Therefore, these investigators were unable to induce sulfite sensitivity by exacerbating airway hyperreactivity.

Cholinergic Reflex. Because sulfur dioxide may produce bronchoconstriction through cholinergic reflex mechanisms, the effect of atropine and other anticholinergic agents has been studied.^{110, 117, 133} Preinhalation of atropine blocked the airway response to oral challenge with sulfiting agents in three of five subjects and partially inhibited the response in two others. Doxepin hydrochloride, which possesses anticholinergic as well as antihistaminic properties, was protective in three of five individuals undergoing oral challenge with sulfites.

Possible IgE-mediated Reactions. Some investigators have attempted to identify an immunologic basis for these reactions. Positive patch tests with sulfites suggested a delayed hypersensitivity mechanism in patients with contact dermatitis.²⁸ The presence of precipitating antibodies to sulfites⁸⁷ or alterations in complement activity¹³⁷ have not been detected. A more likely explanation would be the presence of an IgE-mediated response in selected subjects. Prenner and Stevens observed a positive scratch skin test to an aqueous solution of sodium bisulfite at 10 mg/mL in their patient, who experienced laryngeal edema after sulfite challenge.⁸⁷ This patient also exhibited a dramatic response with intradermal testing at the same concentration. Three nonsensitive control subjects had negative skin tests to sulfites. Of the five asthmatic subjects studied by Stevenson and Simon, none showed positive skin tests to sulfites.¹²⁶ However, the patient of Twarog and Leung, who experienced anaphylaxis after sulfite exposure, showed a positive intradermal skin test response to an aqueous solution of bisulfite at 0.1 mg/mL.¹³⁷ Control subjects were found to have negative skin tests with 1 mg/mL of this solution. Meggs et al reported that a patient developed wheezing when skin tested with sodium bisulfite at 100 µg/mL.⁷⁴ Yang et al identified two asthmatic subjects with either positive prick or intradermal skin tests to sulfites as well as one subject with urticaria and one with anaphylaxis, the latter of whom also was found to have positive intradermal tests to sulfites.¹⁴⁶ Boxer et al reported two additional patients with

positive skin tests and oral challenges to sulfiting agents that induced bronchoconstriction.¹⁷ Selner et al reported positive intradermal and skin puncture tests with 0.1 mg/mL and 10 mg/mL potassium metabisulfite solutions, respectively, in a sulfite-sensitive asthmatic subject.¹⁰⁵ Two nonsensitive control subjects had negative skin tests. Simon also reported two sulfite-sensitive asthmatic patients with positive intradermal skin tests to bisulfites at a concentration of 10 mg/mL, a concentration that did not produce wheal-and-flare cutaneous responses in controls.¹¹⁸ These observations are consistent with an IgE-mediated mechanism, with sulfites acting as a chemical haptens.

Further evidence for an IgE-mediated mechanism is supported by passive transfer experiments (Prausnitz-Küstner transfer). Several investigators have successfully transferred skin test reactivity to nonsensitive subjects with sera from sulfite-sensitive individuals.^{87, 118, 146} Skin-sensitizing activity was abolished by heating the sera to 56°C for 30 minutes.¹¹⁸ Others have not been successful in repeating these experiments.²⁸ These data suggest the presence of a serum factor, presumably IgE, but, to date, specific IgE antibodies to sulfiting agents or sulfiting agents conjugated to human serum albumin have not been successfully demonstrated.^{17, 74} The possibility that sulfiting agents could by themselves stimulate direct mediator release from mast cells or basophils in the absence of IgE has also been considered. Histamine release from mixed peripheral blood leukocytes could not be demonstrated in the five subjects studied by Stevenson and Simon,¹²⁶ but none of the five had positive cutaneous wheal-and-flare responses to sulfites. Simon and Wasserman also found inconsistencies in leukocyte histamine release from peripheral blood leukocytes from a patient whose skin tests to sulfites were positive.¹¹⁸ In contrast, Twarog and Leung found that 20% of the total basophil histamine was released in the patient they studied using concentrations of 10^{-3} to 10^{-7} mol/L sodium bisulfite.¹³⁷ Cells from control subjects did not release histamine. Moreover, the histamine release was enhanced by preincubating the patient's serum with sodium bisulfite.

Similarly, inconsistencies in the measurement of mast cell or basophil mediators in the peripheral blood of challenged patients have been reported. Schwartz did not observe any rise in plasma histamine levels in patients experiencing hypotension and gastrointestinal response during sulfite challenges.¹⁰⁰ Likewise, Altman et al failed to observe changes in serum neutrophil chemotactic activity in sulfite-sensitive individuals during sulfite challenges.⁷ In contrast, Meggs et al observed a significant rise in plasma histamine levels in two of seven subjects with systemic mastocytosis undergoing sulfite challenges.⁷⁴ However, no clinical response was observed. In an asthmatic subject whose skin tests to sulfites were positive, the plasma histamine level tripled during the time of the asthmatic response to sulfite challenge. Four subjects with asthma or rhinitis attributed to sulfite exposure, when challenged intranasally with 5 mg of potassium metabisulfite in distilled water, demonstrated increased histamine levels in nasal lavage fluid 7.5 minutes after the

challenge.⁷⁹ In control subjects with chronic rhinitis, similar results were also obtained, although the level of histamine in nasal secretions was generally less than in the patients with sulfite sensitivity.

Indirect evidence for mast cell mediators playing a roll in the production of bronchoconstriction resulting from sulfiting agents has been reported. Freedman mentions that inhaled sodium cromolyn prevented the asthmatic response to acidic solutions of sulfite.³³ Simon and Stevenson found that inhaled cromolyn inhibited sulfite-induced asthma in four of six subjects and partially inhibited the response in two other subjects undergoing oral challenge with sulfites.¹¹⁷ Schwartz reported that oral cromolyn at a dose of 200 mg blocked an asthmatic response to an oral sulfite challenge in one subject.¹⁰¹

Sulfite Oxidase Deficiency. Simon et al have proposed that a deficiency in the enzyme sulfite oxidase that metabolizes sulfite to sulfate may be responsible for some adverse reactions to sulfites.^{113, 117} Six subjects, found to be sulfite sensitive by oral provocative challenge, exhibited lesser sulfite oxidase activity in skin fibroblasts when compared with normal control subjects. The major source of sulfite oxidase activity in humans, however, is in the liver.

Kinins and Sulfite Sensitivity. While there are as yet no data to suggest a role for the contact system or other kinin-related systems in the pathogenesis of sulfite sensitivity in humans, a report in sheep airways presented evidence for inhaled metabisulfites stimulating bradykinin β_2 -receptors.⁷⁰ Along these same lines, there has been recent evidence of the involvement of tachykinin receptors in the effects of inhaled metabisulfites on guinea pig airways.⁹⁴

Benzoates and Parabens

Benzoic acid and sodium benzoate (benzoates) are widely used as antimycotic and antibacterial preservatives in foods and beverages. To a much lesser extent, the methyl, *n*-propyl, *n*-heptyl esters of parahydroxybenzoic acid, hereafter referred to as parabens (Fig. 3), are also used as preservatives in a limited number of foods and beverages. Parabens, however, are used extensively as preservatives in pharmaceuticals and cosmetics. Benzoic acid, sodium benzoate, methylparaben, propylparaben, and heptylparaben are approved as food and drug additives by the FDA and have been assigned GRAS status.⁴⁷

Benzoates have been used as preservatives in foods and beverages since the early 1900s. With current annual consumption exceeding 10 million pounds by food industries worldwide, they continue to be one of the most commonly used additives. The benzoates have a broad range of antimicrobial and antimycotic activities, exhibit little or no toxicity in the concentrations used, and are relatively inexpensive to produce. Benzoates, in the form of the free acid or as simple salts, esters, and amides, are widely distributed in nature. They occur naturally in prunes, cinnamon, cloves, tea, anise, and many berries. Raspberries and cranber-

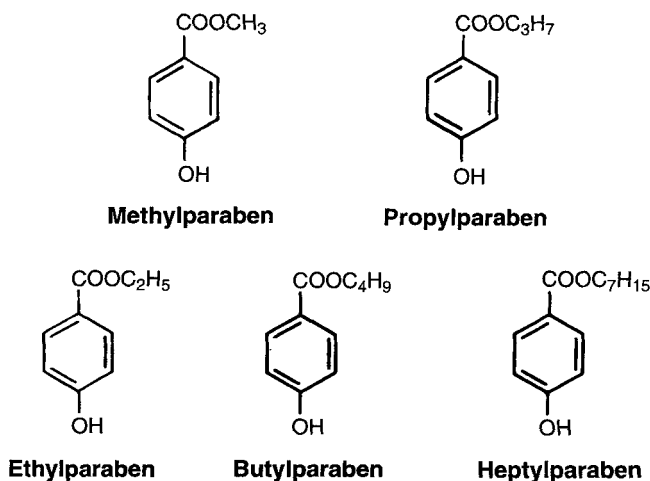


Figure 3. The paraben family of food additives.

ries contain up to 0.05% by weight.^{48, 143} Methylparaben and propylparaben are approved for use as antimicrobial agents in foods such as processed vegetables and baked goods as well as in fats, oils, and seasonings.² They are present in amounts ranging from 0.0001% to 0.10%. Parabens are widely used as preservatives in drugs and are clearly recognized as contactants in contact dermatitis.⁵¹

Monosodium Glutamate (MSG)

Glutamic acid is a nonessential, dicarboxylic amino acid which forms 20% of dietary protein. Glutamate appears naturally in some foods in significant amounts, for example, 100 g of Camembert cheese contains as much as 1 g of MSG; however, the greatest exposure to MSG occurs after it is added to foods as a flavor enhancer. The sodium salt of glutamic acid (MSG) is added to a wide variety of foods by manufacturers, restaurant chefs, and individuals. A Japanese chemist established 90 years ago that MSG was responsible for the flavor-enhancing properties of the seaweed *Laminaria japonica* (traditionally used in Japanese cooking).⁷¹ MSG is routinely added to Chinese, Japanese, and other Southeast Asian foods and soups. Up to 6 g of MSG may be ingested in a highly seasoned Chinese meal. A single bowl of wonton soup can contain 2.5 g of MSG. MSG is also one of the Kentucky Fried Chicken chain's "secret herbs and spices" for its fried chicken. MSG is found in most manufactured meat and chicken products, particularly soup stocks and the increasingly popular diet foods (lean, light, low-calorie, low-fat, or low-cholesterol foods).

MSG currently remains among the GRAS additives listed by the FDA. The fact that MSG is added to a particular food is usually dis-

played on the label. However, the amount of MSG added is seldom revealed. MSG may also appear on a label as "hydrolyzed vegetable protein." The flavor-enhancing properties of MSG stem from its excitatory (depolarizing) action on sensory taste receptors. Current research suggests that adverse reactions are linked to the ingestion of large amounts of MSG, which are rapidly absorbed, particularly when ingested in solutions and on an empty stomach.⁴

Chinese Restaurant Syndrome

Chinese restaurant syndrome (CRS) was first described in 1968 by a Chinese physician, Dr. Robert Homan Kwok, in the *New England Journal of Medicine*.⁶³ This syndrome, occurring within hours of a Chinese restaurant meal, is characterized by headache, a burning sensation along the back of the neck, chest tightness, nausea, and sweating. In 1969, Schaumburg et al reported the first formal study of the effects of MSG in humans.⁹⁷ These investigators suggested that MSG elicits three categories of symptoms: a burning sensation, facial pressure, and chest pain. Headache was considered to be a consistent complaint in only a minority of individuals. Symptoms appeared in susceptible individuals only if the meal contained free MSG and was ingested into an empty stomach. Such individuals responded to 3 g or less of free MSG, an amount found to be present in a 200 mL serving of wonton soup in one New York restaurant.

Schaumburg et al determined that the systemic reactions in their subjects were caused by L-glutamate.⁹⁷ Intensity and duration of symptoms were related to the dosage of MSG. The onset of symptoms was usually 15 to 25 minutes after ingestion. After intravenous administration, the first symptoms appeared in 17 to 20 seconds, with a threshold concentration for inducing minimum symptoms ranging from 25 to 125 mg. In two subjects, intravenous injection of MSG into the forearm, while the circulation was occluded by an axillary cuff, produced a burning sensation over the entire arm. The burning sensation was felt over the chest and neck 17 seconds after the cuff was removed. Schaumburg et al concluded that this burning sensation was a peripheral neuroexcitatory phenomenon and was not due to central nervous system stimulation. Ghadimi et al reported similar findings in 1971 and showed that onset and severity of symptoms are both dose related.³⁸ Subsequent studies of CRS by Kenny and Tidball⁵³ and Reif-Lehrer⁸⁸ suggest that the prevalence of CRS in the population eating in Chinese restaurants is about 30%.

Aspartame

Aspartame (NutraSweet) is a dipeptide composed of aspartic acid and the methyl ester of phenylalanine. It is a low-calorie, artificial sweetener, which is 180 times sweeter than sucrose. It was discovered

serendipitously in 1965 by a chemist seeking to find an inhibitor of gastrin which might function as an anti-ulcer agent.⁷² In 1973, G.D. Searle petitioned the FDA for approval to market aspartame as a sweetener.¹³⁸ In 1974, aspartame was approved for use in dry foods. In December of 1975, the FDA stayed the approval for marketing aspartame due to both concern over problems noted in studies by Searle Laboratories (Chicago, IL) and allegations that aspartame was unsafe and could cause mental retardation and endocrine dysfunction. In July of 1981, the FDA reapproved aspartame as a food additive, and marketing was initiated that same year. In July of 1983, aspartame was approved for use in carbonated beverages.³⁴

Butylated Hydroxyanisole (BHA) and Butylated Hydroxytoluene (BHT)

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are antioxidants that are commonly used in cereal and other grain products. They were originally developed as antioxidants for petroleum and rubber products but were discovered to be effective in preventing oxidation of animal fatty acids in the mid-1950s.⁸ BHT has been promoted by some as an anticancer, antiaging substance and as a treatment for genital herpes.⁸³ Although such claims are largely unsubstantiated, legitimate toxic side effects, including severe gastrointestinal and neurologic toxicities, have been reported after ingestion of standard and suggested doses.^{41, 119}

Nitrates

Nitrates and nitrites are widely used as preservatives. However, their popularity as additives stems from their ability to add flavoring and coloring. These agents are added to processed meats (for example, frankfurters and salamis).

URTICARIA, ANGIOEDEMA, ANAPHYLAXIS, AND ADDITIVES

In 1959, Lockey⁶⁸ first reported three patients with a history of urticaria after the ingestion of tablets containing tartrazine. One patient was in the midst of treatment for a skin eruption caused by another agent. The other two subjects were challenged with tartrazine sublingually in an open manner. One "reacted" (no further description offered). The other had only mild complaints localized to the mouth.

The incidence of reactions to any additives, including tartrazine, in patients with chronic urticaria and angioedema is unknown. This is not due to inadequate numbers of studies but rather to the lack of properly

and vigorously controlled studies and inherent problems in challenging patients with chronic urticaria.

Food Additive Challenge Studies in Urticaria Patients

Design Considerations

Patient Selection. Selection of patients for study may include 1) all available patients with chronic urticaria (or only those with chronic idiopathic urticaria), 2) only those with histories suggestive of food additive-provoked urticaria, or 3) those whose urticaria improved after a diet free of commonly implicated additives. Depending upon the group selected and the challenge process, different percentages of so-called positive reactors have been reported. These variables, often omitted or poorly stated in reports and studies, add more confusion to the already difficult task of comparing results between different studies.

Activity of Urticaria at the Time of Study. The relative degree of activity or inactivity of urticaria or angioedema at the time of challenge appears to determine the ability of the skin to respond with cutaneous reactions during subsequent additive challenges. Patients with active urticaria are more likely to develop further urticarial activity, while challenges performed upon patients whose urticaria is in remission are more likely to yield negative results. In the study of Lumry et al, only 1 of 15 patients whose urticaria was in remission experienced a reaction to aspirin (ASA), whereas 7 of 10 patients whose urticaria was active at the time of challenge reacted to ASA.⁶⁹ These challenges were conducted using objective reaction criteria, and reactions were compared with those observed during a baseline observation period in the same patient.

Medications. In several studies, a reference is not made as to whether medications, particularly antihistamines, are continued or withheld during challenges. However, the important caveats to bear in mind when interpreting challenge studies that mention details of withdrawing medications are 1) discontinuation of antihistamines immediately before or within 24 hours of challenge is likely to induce false-positive reactions, 2) continuation of antihistamines during challenges may block some of the milder additive-induced cutaneous responses and therefore promote false-negative results, and 3) subjects are also more likely to experience breakthrough urticaria the longer the interval from last antihistamine dose to the test substance associated with a "positive challenge." This last phenomenon is accentuated if placebo controls are given first, before additive challenges, and in closest proximity to the protective effect of the last antihistamine tablet.

Reaction Criteria. In most studies, a period of baseline observation for comparison with reaction data was never undertaken. Most challenge studies reported loosely defined and subjective criteria for identifying urticarial response. The reaction criteria simply consisted of "clear signs of urticaria developing within 24 hours." The studies by Stevenson et

al¹²⁷ and Lumry et al⁶⁹ represent the only reported challenge studies that utilized an objective system of scoring urticarial responses.

Placebos. The importance of placebo-controlled studies in additive challenges cannot be overemphasized. Studies not utilizing placebo controls are useless in specifically linking urticarial responses to a challenge substance. There are a surprising number of published studies of additive challenges that never employed placebo controls. Even in most placebo-controlled studies, the placebo was usually the first challenge substance, followed by ASA and then an additive. Thus, a spontaneous flare of urticaria was least likely to coincide with the first placebo challenge, particularly if antihistamine was last ingested just before beginning challenges. The use of multiple placebos, including randomization of placebos, enhances the design of placebo-controlled challenges and eliminates the bias of first-challenge placebo alone.

Controls. Among the most important features of any food additive challenge protocol is a double-blind challenge. Because exacerbation of urticaria may be provoked by stress, it is necessary to blind the study subjects. Furthermore, nurses and physicians can transmit unspoken signals of concern and apprehension when the "real" test substance is administered. Finally, it is important to eliminate observer bias whenever possible because positive responses always consist of the appearance of hives or hives in greater numbers than were observed at the baseline level.

Doses. Table 3 lists maximum doses for common additives implicated in adverse reactions. Starting doses should be individualized depending upon estimated amount ingested at the time of reported reaction, the severity of reaction, and the level of sensitivity. Initial doses are usually doubled at maximum recommended levels.

Multiple Additive Challenges in Chronic Urticaria

Examples of Studies with Less Stringent Design Criteria. One of the earliest open additive challenge studies in chronic urticaria patients was reported by Doeglas.²⁷ He found that 7 of 23 patients (30.4%) reacted to tartrazine and "four or five" (17.4% or 22.7%) reacted to sodium benzoate. Placebo-controlled challenges were not performed. Thune and

Table 3. SUGGESTED MAXIMUM DOSES FOR ADDITIVES USED IN CHALLENGE PROTOCOLS

Additive	Dose (mg)
Tartrazine	50
Sulfites	200
MSG	5
Aspartame	150
Parabens/benzoates	100
BHA/BHT	100

Granholt¹³⁵ reported that 20 of 96 patients reacted to tartrazine, 13 of 86 reacted to sunset yellow (FD&C Yellow No. 6) dye, 5 of 7 reacted to parabens, and 6 of 47 reacted to BHA and BHT. Furthermore, in their total group of 100 patients with chronic idiopathic urticaria, 62 of the 100 reacted to at least 1 of the 22 different additives used in challenges. Because none of the challenges were placebo controlled, conclusions about the specificity of reactions, linked to a particular additive, are difficult to support.

In a study of 330 patients with recurrent urticaria, Juhlin performed single-blind challenges using multiple additives⁴⁹ and only a single placebo, which was always given first, preceding the additive challenges. He found one or more positive reactions in 31% of patients challenged. Reaction criteria were subjective. Reactions were judged to be "uncertain" in 33% of patients because, as the author stated, "judging whether a reaction is positive or negative is not always easy." Furthermore, if patients "reacted" to the lactose placebo, a wheat starch placebo was then used in retesting, presumably because the author assumed that the original burst of urticaria was due to the placebo. Questionable reactors were retested, and if the repeat test was positive, it was assumed that the first test was positive; the same logic applied for retesting with a negative response.

Supramaniam and Warner¹³⁰ reported that 24 of 43 children reacted to one or more additives in their double-blind challenge study. However, a baseline observation period was not undertaken, and only one placebo was interspersed among the nine different additives used as challenge substances. Furthermore, whether antihistamines were withheld prior to or during challenges was not mentioned.

In 1985, Genton et al³⁵ performed single-blind additive challenges on 17 patients with chronic urticaria and angioedema of unknown type. All medications were discontinued at the beginning of the diet, and patients were subjected to a 14-day elimination diet (free of food additives) before any challenges. Of the 17 patients, 15 developed urticaria after at least one of the six additives used for challenge in this study.

Examples of Studies with Better Design and Reaction Criteria.

Recently, Ortolani et al⁸⁰ studied 396 patients with recurrent chronic urticaria and angioedema as a follow-up to a study performed in 1984.⁸¹ Double-blind, placebo-controlled, oral food provocation challenges were performed on patients who had significant remissions in their urticaria while following an elimination diet. Medications were discontinued during challenges, but the timing of discontinuation of medications was not mentioned. Based on history alone, 179 patients were considered for, but only 135 patients participated in, an elimination diet for suspected food or food additive intolerance. Only 8 of 87 patients who reported significant improvement on the 2-week elimination diet had positive challenges to foods. Of the 79 patients with negative food challenge, 72 underwent double-blind, placebo-controlled, oral food additive provocation challenges. Twelve patients had positive challenges to one or more additives; many of these patients were reported to have

reacted to two or three of the test additives. Five of 16 patients with positive ASA challenges had positive additive challenges; the challenges in 4 of these patients were due to sodium salicylate. The similarity in chemical structure between ASA and sodium salicylate supports the concept of cross-reactivity between ASA and sodium salicylate; however, the doses used (>400 mg) in the sodium salicylate challenge far exceeded those encountered in conventional diets and therefore had little to do with native dietary exposure. Considering that the proposed mechanisms for reactions to additives such as tartrazine, sodium benzoate, and sulfites are so different, the meaning of "positive challenges" in this study is unclear. Furthermore, although a patient's history is important to the consideration of food sensitivity, it is usually a poor indicator of a possible additive hypersensitivity because patients are usually not aware of all the additives they consume daily and are always reporting urticarial flare-ups in relation to external events and ingestions. Elimination of more than 50% of the original study population may have been proper for food sensitivity determinations, but it was not justified for selection of patients for additive challenges.

Hannuksela and Lahti⁴⁶ challenged 44 chronic urticaria patients with several food additives, including sodium metabisulfite, BHA and BHT, β -carotene, and benzoic acid, in a prospective, double-blind, placebo-controlled study. Only 1 of 44 patients had a positive challenge (to benzoic acid). However, 1 of 44 patients also reacted to a placebo challenge. All medications were discontinued 72 hours before the first challenge and during the study. Patients were not following an additive-free diet before the challenges. The challenge dose of metabisulfite was quite low (only 9 mg). Similarly, Kellett et al⁵² noted that approximately 10% of 44 chronic idiopathic urticaria patients reacted to benzoates and tartrazine, but 10% of the same population also reacted to placebos.

Studies of Elimination Diets. An alternative way to investigate urticaria, which is presumed to be secondary to food additives, is to eliminate all additives from the diet and then observe a decrease in hives. Unfortunately, blind or placebo-controlled studies of this type have not been reported in the literature. In uncontrolled studies, Ros et al⁹¹ reported an additive-free diet to be "completely helpful" in 24% of patients with chronic urticaria. Another 57% of patients were "much improved," and 19% were "slightly better" or experienced "no change" in their urticaria. Rudzki et al⁹³ reported that 50 of 158 patients responded to a diet free of salicylates, benzoates, and azo dyes. These studies did not address the question as to which, if any, additives had been inducing urticaria.

In another study, Gibson and Clancy³⁹ found that 54 of 76 patients who underwent a 2-week additive-free diet "responded." Using the same study population, they then challenged the respondents with individual additives. Although the challenges were placebo controlled, the placebo was always given first. Furthermore, no mention was made as to whether the challenges were blinded. A diet free of the offending additive was then continued for 6 to 18 months, followed by a repeat

challenge. None of the 3 patients who initially experienced a positive challenge after tartrazine developed urticaria upon rechallenge with tartrazine 6 to 18 months later. One of the 4 patients with initially positive benzoate challenges also experienced a negative challenge upon re-exposure 6 to 18 months later. Therefore, despite a dietary elimination approach, the incidence of additive-induced urticaria continues to be elusive.

Reports of Additive Sensitivity Using Single or Limited Challenges

Tartrazine (FD&C Yellow No. 5). Even the incidence of reactions to tartrazine, the most commonly implicated additive causing reactions in patients with urticaria, is not known. In a double-blind, placebo-controlled study, 3 of 38 patients with chronic urticaria (8%) reacted to tartrazine.³⁹ All 3 patients were likely sensitive to ASA; however, the details of the challenge protocols were not presented, and the challenge dose of tartrazine was only 0.22 mg. The choice of challenge dose was based on quantity of tartrazine added to pharmaceutical tablets. Much greater amounts of tartrazine are found in foods and drinks (25 to 50 mg).

Settipane and Pudupakkam¹⁰⁶ report tartrazine sensitivity in some patients with urticaria who were also sensitive to ASA. However, in a single-blind study of the incidence of ASA sensitivity in chronic idiopathic urticaria at the Scripps Clinic, we administered 25- and 50-mg doses of tartrazine (up to a total dose of 75 mg in most patients during 1 challenge day), and only 1 of 24 patients reacted with urticaria. This single suspected tartrazine reactor was then rechallenged using a double-blind, placebo-controlled tartrazine challenge and again developed urticaria after 25 mg of tartrazine.¹²⁷ This patient did not experience any reaction to ASA (receiving a total of 975 mg, with 650 mg as a final single dose) and gave an excellent history of reported urticaria after previous exposure to tartrazine in her diet.

Sunset Yellow (FD&C Yellow No. 6). A single case report described a 43-year-old physician with acute episodes of severe abdominal pain and hives believed to be secondary to FD&C Yellow No. 6 dye. Despite ongoing ingestion of this dye, the subject experienced only four isolated episodes of hives in 2 years. Two challenges, one single and the other double blind, provoked "reactions." The single-blind challenge was associated with both abdominal pain and urticaria; however, the double-blind challenge was only associated with pain and not with urticaria.⁴²

Sulfites. In 1976, Prenner and Stevens reported the occurrence of an anaphylactic reaction after the ingestion of food sprayed with sodium bisulfite.⁸⁷ The patient, a 50-year-old man, experienced generalized urticaria and pruritus, swelling of the tongue, difficulty in swallowing, and tightness in his chest within minutes after eating lunch at a restaurant. He responded promptly to treatment with subcutaneous epinephrine. Subsequently, a prick test to sulfite and an intradermal test were signifi-

cantly positive (with negative controls). The authors were able to demonstrate passive transfer, via Prausnitz-Küstner testing, to a nonatopic human recipient.

In 1980, Clayton and Busse²⁴ described a nonatopic female who developed generalized urticaria that progressed to life-threatening anaphylaxis within 15 minutes of drinking wine. Her symptoms were not reproduced by ingestion of other alcoholic beverages. In retrospect, this may have been a case of sulfite-provoked urticaria and anaphylaxis.

Habenicht et al⁴⁴ described two patients with several episodes of urticaria and angioedema following restaurant meals. Only one of these patients underwent a single-blind oral challenge with potassium metabisulfite; generalized urticarial lesions developed within 15 minutes of the 25-mg challenge dose. However, a placebo challenge was not performed. Avoidance of potential sulfite sources apparently has led to resolution of this patient's recurrent symptoms.

Schwartz reported two patients with restaurant-related symptoms who underwent oral metabisulfite challenges.¹⁰⁰ Both patients had symptoms, including weakness, a feeling of dissociation from body, dizziness, nausea, chest tightness, and possible hives, temporally related to ingestion of salads. Upon challenge, both patients experienced abdominal distress, dizziness, borderline hypotension, and bradycardia. These signs and symptoms were more consistent with vasovagal reactions than with anaphylaxis. In a 1985 report, Schwartz described a patient who received less than 2 mL of procaine (Novocaine) with epinephrine subcutaneously.¹⁰³ Within several minutes, she developed a sense of flushing, warmth, and pruritus, followed by scattered urticaria, dyspnea, and a sense of anxiety. Skin tests, using various local anesthetics and sulfite, were negative. She developed "a sense of fullness in her head, nasal congestion, and a pruritic erythematous blotchy eruption" 30 minutes after a single-blind oral dose of 10 mg of sodium bisulfite. Respiratory symptoms did not develop and pulmonary function test results remained normal. This patient went on to tolerate the same local anesthetics without epinephrine. It is critical to note that this patient did not describe a history of food-related symptoms. Furthermore, the usual dose of aqueous epinephrine (Adrenalin) contains only 0.3 mg of sulfite, and local anesthetics contain only up to 2 mg/mL of sulfite. Therefore, usual doses of such anesthetics, even in the most sensitive individuals, would not be expected to provoke reactions. The mechanism of this patient's "reaction" cannot be confidently linked to sulfite and was likely a vasomotor response secondary to anxiety and to the effects of epinephrine.

There are now two publications demonstrating the inability of investigators to provoke reactions to sulfites in patients with idiopathic anaphylaxis, some with histories of restaurant-associated symptoms.^{62, 120} In a study describing food skin testing in 102 patients with idiopathic anaphylaxis, only 1 patient was found to have cutaneous sensitivity to metabisulfite.¹²⁸ In addition, we have performed sulfite ingestion challenges in 25 patients with chronic idiopathic urticaria and angioedema

without encountering any reactions. Therefore, except for the reports by Prenner and Stevens⁸⁷ and Yang et al,¹⁴⁶ no other studies using properly controlled challenges confirm sulfite-induced urticaria, angioedema, or anaphylaxis. Yang et al described 1 patient with a history of sulfite-provoked anaphylaxis.¹⁴⁶ A borderline intradermal skin test was demonstrated, as was a positive single-blind oral provocation challenge to 5 mg of potassium metabisulfite. This patient's cutaneous reactivity was also passively transferred via the Prausnitz-Küstner reaction. However, these investigators were unable to elicit positive challenges in 9 patients with histories of hives after eating restaurant food. In conclusion, IgE-mediated immediate hypersensitivity reactions to sulfites (possibly via a hapten recognition) appear to be extraordinarily rare, if they exist at all, in inducing urticaria and anaphylaxis. In the overwhelming majority of cases, the mechanism of sulfite-provoked urticaria, angioedema, and anaphylaxis (or anaphylactoid reactions) remains an enigma.

Benzoates and Parabens. There are no individual reports that discuss a relationship between these agents and urticaria or angioedema. In the literature, we are aware of a total of two reports (three cases) of apparent IgE-mediated, paraben-induced urticaria and angioedema.^{3, 76} Benzoates in pharmaceutical preservatives were the presumed source of these additives. All three patients had positive skin tests to parabens but not to the drugs themselves, which were free of paraben preservatives. These patients were able to tolerate oral benzoates in their diet without reaction. Thus, the mechanism of paraben- and benzoate-induced urticaria does not appear to be adequately explained by classic IgE-mediated immediate hypersensitivity to these compounds.

MSG. A 1987 letter in the *Lancet*⁴³ described a 50-year-old man with recurrent angioedema of the face and extremities, which was related by history to ingestion of a soup that contained MSG. A single-blind, placebo-controlled challenge with the soup base resulted in "a sensation of imminent swelling" within a few hours, but visible angioedema appeared 24 hours postchallenge. In a graded challenge, angioedema occurred 16 hours after challenge with 250 mg of MSG alone. Avoidance of MSG led to an extended remission. Details of the challenge were not reported nor was there any mention of whether medications were withheld during challenges.

Aspartame. Two cases of aspartame-provoked urticaria and angioedema have been reported.⁶² In both individuals, hives began after aspartame was approved as a sweetener in carbonated beverages in 1983. Both patients reported the onset of urticaria within 1 hour of ingesting aspartame-sweetened soft drinks. Double-blind, placebo-controlled challenges reproduced urticaria with doses of aspartame (25 to 75 mg) below the amount contained in a typical 12-ounce can (100 to 150 mg). Despite the widespread use of aspartame in diet drinks and elsewhere, other reports have not followed to confirm these initial findings. Even an attempt to recruit patients believing themselves to be sensitive to aspartame did not yield additional subjects for challenge studies.⁷⁶ In this study, 12 subjects with urticaria but without a history

of aspartame-associated urticaria were challenged with aspartame, and none experienced a reproducible adverse reaction.

BHA and BHT. Roed-Petersen and Hjorth found four patients with eczematous dermatitis who had positive patch tests to BHA and BHT.⁹⁰ Dietary avoidance of the antioxidants resulted in remissions in two patients. When challenged with ingestion of 10 to 40 mg of BHA or BHT, both patients experienced exacerbations of their dermatitis. Osmundsen reported a case of contact urticaria, apparently due to BHT contained in plastic folders; the patient had positive wheal-and-flare responses to 1% of BHA and BHT in ethanol.⁸² A case of acute urticarial vasculitis related to BHT in chewing gum has also been reported.⁷⁵

Recently, two patients with chronic idiopathic urticaria, in whom remissions were achieved while following dye and preservative elimination diets, had exacerbations of their urticaria when challenged under double-blind, placebo-controlled conditions with BHA and BHT.⁴⁰ After elimination of BHA and BHT from their diets, the patients were observed to have marked abatement of the frequency, severity, and duration of their urticaria.

Summary

Tartrazine and other dyes, benzoates, and parabens may occasionally aggravate chronic urticaria but have not been reported as the cause of the condition. Parabens have been shown to provoke (rarely) anaphylaxis when given parenterally. Sulfites, although not implicated in chronic urticaria, have occasionally been reported to provoke anaphylaxis. MSG has been reported to provoke angioedema in a single case report. Aspartame, BHA, and BHT have been shown to be the cause of isolated cases of chronic idiopathic urticaria. Nitrates and nitrites have not been associated with urticaria, angioedema, or anaphylaxis.

ASTHMA AND ADDITIVES

Design Considerations for Challenge Studies

General Considerations

A screening challenge should be conducted in a single-blind, open fashion. Because so few patients are sensitive to additives, single-blind challenges simplify the procedure. More importantly, such a challenge fulfills the safety requirement of individualizing doses. At each successive challenge step in the protocol, the doses increase twofold. If a patient has a 10% to 15% drop in FEV₁ after a particular dose, it may be advisable to add a dose at half the usual increment of increase. This would not be possible with a double-blind challenge protocol.

Other safety factors include performing the challenge when the

patient's asthma is stable (FEV₁ value of at least 1.5 L and 70% of predicted or prior best values). At times, especially in patients most likely to be sulfite sensitive (for example, chronic asthmatic patients, who are corticosteroid dependent), these patients may require a burst of corticosteroids to stabilize their asthma activity (as in ASA-sensitive subjects). Challenges routinely begin in the morning and can take place in the physician's office if one is prepared to treat rapidly moderate to severe asthma with inhaled bronchodilators. Using the recommended protocol and individualized doses, we have not encountered any severe reactions during hundreds of sulfite challenges, and all patients' bronchoconstriction could be rapidly reversed with albuterol or metaproterenol administered with a handheld nebulizer.

On the day of challenge, patients should withhold their inhaled and oral β -agonists and inhaled anticholinergics, and antihistamines and cromolyn should be withheld for 24 hours before the challenge. We continue theophylline at therapeutic levels and continue (even increase) levels of inhaled and oral steroids. In our experience, theophylline and steroids do not interfere with sulfite (or ASA) challenges.^{84, 116, 126} Although a recent study suggests that corticosteroids may increase the threshold reaction dose,⁷⁸ withholding theophylline and steroids may lead to a false-positive challenge in an unstable asthmatic patient. To control this variable, and to establish stability of their bronchial airways, we recommend that patients undergo a placebo challenge for a length of time equal to that of the sulfite challenge.

Pulmonary function is measured before challenge and before the next dose or sooner if symptoms occur. A 20% drop in FEV₁ value from the baseline level is considered to be a positive challenge.

Sulfite Challenge

Specific Considerations

Since the FDA regulation on sulfite usage in the late 1980s, the indications for challenges with sulfur dioxide, sulfite, and sulfurous acid particles have become limited to scientific investigation and very occasional clinical purposes. Challenges for investigation of the environmental and occupational hazards of sulfur dioxide and sulfuric acid exposures include epidemiological studies and studies of asthmatic populations aimed at better drawing the lines for regulating emissions of these chemicals.¹⁵ Likewise, scientific investigations aimed at better understanding the bronchial hyperreactivity associated with asthma may employ sulfur dioxide or sulfite challenges akin to histamine, methacholine, exercise, water, osmolar, allergen, mediator, and pharmacological challenges outlined in other articles in this issue.

For clinical purposes, when an asthmatic patient recognizes reactivity to sulfur dioxide and sulfite, as is most likely to occur with exposure to or ingestion of dried fruits or wine, that individual can avoid these

sulfite sources and is further protected by regulations of the FDA requiring labeling of processed food containing > 10 ppm of sulfur dioxide equivalents. If there is suspicion, particularly if there is uncertainty regarding reaction to dried fruits, wine, processed potatoes, or shrimp, or when reassurance is needed that an asthmatic patient is not relevantly sensitive to sulfites, oral challenge with the suspected food or beverage¹³⁴ or capsule doses of sulfite under single-blind (and if the result is apparently positive, then double-blind) conditions are appropriate.

At the Scripps Clinic, we use the following protocol for sulfite capsule challenges: patients are challenged at a time when their asthma is in remission as documented by FEV₁ greater than 70% of the predicted or best previously observed value and at least 1.5 L absolute. Inhaled cromolyn⁵⁵ and anticholinergic,¹¹⁴ antihistamine,¹¹⁵ and adrenergic bronchodilator medications are withheld on the day of challenge; other medications are continued. Open oral challenges with capsule doses of 5, 25, 50, 100, and 200 mg of potassium metabisulfite at 30-minute intervals are administered, and spirometric measurements are performed before each dose. If there is a fall of FEV₁ of 20% or more, the challenge is suspended, and obstruction is reversed with inhalations of adrenergic bronchodilator. Apparent reactions need to be verified with double-blind, placebo-controlled challenges.

Before concluding that a patient is sulfite sensitive, one should repeat the challenge in a double-blind, placebo-controlled manner, starting with the patient's previously established provoking dose and using at least two other placebo challenges. For suggested challenge doses for common food additives, see Table 3.

Specific Additives and Asthma

Tartrazine

Data on the incidence of reactivity to additives in patients with asthma are, on the whole, only slightly better than those for patients with urticaria. The additive most frequently implicated in provoking asthmatic reactions has been tartrazine. Critical review of the medical literature, however, suggests that sensitivity to tartrazine in patients with asthma is distinctly unusual, if it exists at all.^{111, 125} In 1958, Speer¹²² stated that agents used in artificial coloring were the cause of asthma in sick children; however, the author presented no details about how this conclusion was reached. In 1967, Chafee and Settignano²¹ reported a patient with severe asthma who experienced angioedema after ASA ingestion and severe attacks of asthma shortly after ingesting a number of unrelated drugs. After approximately 2 years of such reactions and a great deal of investigative activity, the attacks disappeared when benzoates and tartrazine were eliminated from this patient's food and medication. During eight double-blind, placebo-controlled challenges with various dyes, significant symptoms (tickling of throat, tight cough, and

wheezing) occurred only after receiving tartrazine. Unfortunately, no pulmonary function studies were conducted, and the double-blind challenge for tartrazine was not repeated.

In their classic monograph on ASA intolerance, Samter and Beers⁹⁶ discussed the fact that benzoates and tartrazine were commonly used in the food ingested by their ASA-sensitive subjects. In their first report, 80 patients with asthma were challenged with unknown doses of tartrazine, and 3 "reacted."⁹⁵ However, essential information concerning withholding or continuing medications, use of placebo controls, and criteria for positive reaction were not provided. Juhlin et al⁵⁰ reported that 7 of 8 patients with asthma who were sensitive to ASA also reacted to tartrazine. However, the investigators' criteria for a positive reaction were subjective, and details of the placebo challenges were not discussed. As the studies of Stenius and Lemola¹²⁴ point out, such details are important. Their protocol called for withholding bronchodilators on the day of challenge, then giving a placebo first, followed by ASA and finally tartrazine. All these challenges took place on the same day; therefore, any patient requiring bronchodilators would be least likely to "react" to the placebo and more likely to "react" to ASA. Finally, as the day wore on and any possible bronchodilator effects wore off, patients' bronchial trees became most likely to constrict, in the absence of bronchodilators, or to "react" to tartrazine. It is also unclear from these studies what happened to the patients who "reacted" to ASA; that is, when exactly was the tartrazine challenge performed in the sequence of challenges? Was it performed after treatment for the ASA reaction, after the ASA reaction spontaneously resolved, in the midst of an unresolved ASA reaction, or on another day? In view of any of these uncertainties, how would one interpret a "reaction" to tartrazine? Finally, the criteria for a positive reaction was a 20% drop in peak expiratory flow. Their data were also inexactly reported: "about 25% of 140 asthmatics were aspirin-sensitive and 20% tartrazine-sensitive."

In another study without placebo controls, Freedman³² challenged 14 of 30 patients with asthma who gave a history of asthma after ingestion of orange-colored drinks. Only one patient experienced a "reaction" to tartrazine; her maximal fall in FEV₁ was only 14% after ingestion of a 20-mg dose (apparently the criterion for a reaction was a 14% decline in FEV₁ values). In a more recent study by Rosenhall,⁹² 2.3% of 542 patients with asthma had a "definitely" positive response to tartrazine, and another 6% had a "probably" positive response. Some problems with this study included single-blind challenges and the fact that placebo studies were conducted only if challenges to other substances were "difficult to interpret." Furthermore, nonrespiratory tract changes, including cutaneous responses such as urticaria and gastrointestinal complaints such as vomiting or diarrhea, were included as criteria for a positive response in these asthmatic subjects.

A decade earlier, one of the few double-blind, placebo-controlled challenges with tartrazine was performed in 38 patients with a history of ASA-provoked asthma.¹⁰⁶ Although only 0.44 mg of tartrazine was

used as the highest provoking dose, 3 of 38 patients were found to be responsive to tartrazine (experiencing a >20% decline in vital capacity, FEV₁, and expiratory flow rates).

Spector et al¹²¹ performed placebo-controlled ASA and tartrazine challenges in more than 200 patients. Of 230 patients, 44 had positive reactions to ASA (an incidence of almost 20%). Of 277 patients, 11 reacted to tartrazine (FEV₁ drops of >20%), an incidence of less than 4% in the population studied; however, 5 of these 11 patients did not undergo placebo challenges. All 11 patients who were reported to have reacted to tartrazine also had a reaction to ASA during another challenge. In other words, tartrazine sensitivity was not observed in patients with asthma who were not sensitive to ASA. One could extrapolate from these data that 15% to 25% of ASA-sensitive asthmatic patients are also sensitive to tartrazine. Yet in double-blind, placebo-controlled challenges of 45 patients who had a history of moderately severe asthma (one half of whom also had nasal polyps and up to 45% of whom were sensitive to ASA), Weber et al¹⁴² did not find any who were sensitive to tartrazine in doses up to 20 mg. Along these lines, Vedanthan et al¹⁴¹ conducted tartrazine challenges in 54 children (aged 10 to 17 years) with asthma and found none who were sensitive to tartrazine. Five of the 54 children were sensitive to ASA during challenges conducted at another time.

Tarlo and Broder¹³¹ performed double-blind ingestion challenges with tartrazine, benzoate, and ASA. Of 28 subjects, only 1 responded to tartrazine (15 mg producing a 20.4% drop in FEV₁) and 1 to benzoate (25 mg provoking a 29% drop). Neither of these patients was found to be ASA sensitive during challenges with this drug, and neither responded to dietary elimination of the two suspected additives.

In 1985, Genton et al reported challenge results with additives, including tartrazine, in 17 asthmatic subjects.³⁵ Attempts were not made to mask flavor or color of the agents tested. β -agonists were withheld, and only a single placebo was administered versus multiple doses of other substances. A positive challenge was defined as a 20% drop in peak flow rates up to 8 hours after a challenge. Even with this protocol, only 1 subject "reacted" to tartrazine.

For more than 20 years, investigators at the Scripps Clinic have been studying ASA-sensitive asthma. One should note that tartrazine is not a cyclo-oxygenase inhibitor³⁶ and therefore would not be expected to cross-react with ASA, as do nonsteroidal, anti-inflammatory drugs, in such patients. In any case, we performed tartrazine challenges before ASA challenges as a routine procedure in more than 150 single-blind, placebo-controlled challenges (with 25 and 50 mg of tartrazine) in our ASA-sensitive asthmatic population. In this single-blind screening study, we identified six patients whose FEV₁ declined after tartrazine.¹²⁵ In five of six patients, rechallenge with tartrazine using double-blind, placebo-controlled challenge sequences were negative. One patient who experienced a decline in FEV₁ values during single-blind tartrazine challenges moved out of town, and we have been unable to rechallenge this patient in a double-blind, placebo-controlled fashion. We remain skeptical that

tartrazine-induced asthma attacks even exist. Certainly, evidence linking tartrazine to ASA sensitivity has not been forthcoming.

Other Dyes

Reactions to non-azo dyes and azo dyes other than tartrazine are far less commonly reported than those to tartrazine, even in those studies that reported tartrazine sensitivity. Therefore, these agents will not be discussed further.

Sulfites

In 1973, Kochen described a child who developed acute bronchospasm after opening cellophane packages and ingesting dried fruits treated with sulfur dioxide.⁵⁴ Although the term *sulfite* was not mentioned, this report may in fact be the first example of sulfite inhalation-induced asthma. The first case report actually specifying sulfite was in 1976 by Prenner and Stevens.⁸⁷ They described a nonasthmatic but atopic individual with a history of hay fever. After a sulfite-containing restaurant meal, the subject developed generalized urticaria, angioedema, and possibly laryngeal edema. During an unlinked oral challenge with a 10-mg sulfite capsule, the patient developed itching, cough, and tightness in the throat. The challenge was considered to be positive and was discontinued without producing urticaria, angioedema, or laryngeal edema. Pulmonary function tests to determine whether there was an asthmatic response were not performed.

In 1977, Freedman, in the United Kingdom, noted that many asthmatic patients gave histories of reacting to citrus drinks.³² These drinks contain tartrazine (FD&C Yellow No. 5) and benzoate as well as sulfur dioxide. Freedman's "sulfur dioxide challenges" were performed by having subjects ingest solutions into which sulfites had been dissolved. Some of the asthmatic subjects did have wheezing after sulfur dioxide challenges. However, the challenges were not placebo controlled, and the amount of sulfur dioxide inhaled is not clear. The author considered a drop in FEV₁ of as little as 12% to be a positive reaction.

In 1981, Stevenson and Simon first reported 5 adult asthmatic patients with a history of severe restaurant-provoked asthma, and even anaphylaxis, who underwent single-blind, placebo-controlled capsule challenges. A 20% or greater drop in FEV₁ 10 to 20 minutes after ingesting capsules containing 5 to 50 mg of potassium metabisulfite (K₂S₂O₅) was reproduced in all 5 patients during single-blind oral challenges.¹²⁶ Simultaneously, Baker, Collette, and Allen reported asthmatic reactions to sulfites contained in pharmaceutical products.⁹ In 1982, Twarog and Leung observed an 18-year-old asthmatic subject with a history of recurring asthma attacks after restaurant meals.¹³⁷ In addition, on two separate occasions while hospitalized for nonasthma-related problems, the patient received isoetharine (Bronkosol) and experienced severe attacks of asthma resulting in respiratory arrest. This patient

also developed an equally severe reaction after receiving intravenous metoclopramide (Reglan). Comparison of the constituents of these two agents revealed bisulfite as the only common substance. A patient with a similar paradoxical bronchospastic reaction following Bronkosol inhalation was reported in 1983 by Koepke et al.⁵⁷ Genton et al found 4 of 17 adult asthmatics who reacted to high concentrations of acidic solutions of sulfites.³⁵ Also in 1985, Schwartz and Scher described in a letter a patient who experienced episodes of bronchoconstriction after application of an eye solution containing sulfite preservatives.⁹⁹

Clinical Characteristics of Sulfite-Sensitive Asthmatic Individuals

Patient Profile

The typical clinical features of sulfite-sensitive asthmatic individuals were first described in 1981.¹²⁶ All have chronic asthma, usually are corticosteroid dependent, and are provoked by multiple other factors (for example, upper respiratory infections, irritants, and exercise). The irritant effects of smog, presumably on afferent receptors in the trachea, are particularly troublesome for these individuals. Characteristically, the most severe corticosteroid-dependent, sulfite-sensitive subjects did not have asthma until their first isolated sulfite reactions. Within months, they progressed from asymptomatic to chronic asthma with corticosteroid dependency. This indicates that any member of the population is at risk for sulfite sensitivity. The typical sulfite-sensitive asthmatic individual is usually nonatopic with chronic vasomotor-type rhinosinusitis. These individuals are differentiated from ASA-sensitive patients because they lack nasal polyps and eosinophilia. Sinus radiographs are abnormal in a high percentage of both ASA-sensitive and sulfite-sensitive asthmatic individuals.

Cross-Sensitivity

Studies by Stevenson and Simon in 15 sulfite-sensitive asthmatics showed that none reacted to ASA during oral challenges and, vice versa, that none of a group of 15 ASA-sensitive asthmatic subjects had positive oral sulfite challenges.¹¹⁶ Moreover, careful review of the medical literature does not confirm that ASA and sulfite sensitivity coexist in the same individual. One report described dual positive challenges in some patients with chronic asthma.⁵⁴ However, the details of the challenges and the clinical characteristics of the patients were not available in the report. One sulfite-sensitive asthmatic patient originally described as ASA sensitive⁵⁷ was subsequently rechallenged with both ASA and sulfite at the Scripps Clinic and found to have only sulfite sensitivity.¹¹² None of our sulfite-sensitive asthmatic patients have experienced posi-

tive challenges to tartrazine (50 mg) or MSG (2500 mg) nor have they manifested IgE-mediated sensitivity with food antigens by skin testing.

Although Baker and colleagues described sulfite-sensitive patients who also had sensitivity to ASA and, in some cases, other additives such as MSG and benzoates, these data were largely historical and not confirmed by challenges.⁹ In addition, the dose of sulfite used during their challenges was 500 mg. We now recognize that this dosage is excessive. Finally, one report described an individual with a history of MSG sensitivity who reacted to both MSG and sulfite (50 mg in solution) in a double-blind, placebo-controlled challenge.⁵⁹

Prevalence

The prevalence of adverse reactions to sulfiting agents is not known, despite attempts to establish the prevalence of sulfite sensitivity in asthmatic subjects. Because of the nature of the populations studied and the challenge methods employed, the incidence can only be estimated. In a preliminary study, Simon et al examined the prevalence of sensitivity to ingested metabisulfite in a group of 61 adult asthmatic subjects.¹¹⁵ None gave a history of sulfite sensitivity. Challenges were conducted with potassium metabisulfite capsules and solutions. Positive responses were confirmed by a placebo-controlled challenge. Of 61 patients, 5 (8.2%) had a 25% or greater decline in FEV₁ values during sulfite challenge. Koepke and Selner conducted open challenges with sodium metabisulfite in 15 adults with a history of asthma after ingestion of sulfited foods and beverages.⁵⁸ One of the 15 subjects (7%) had a 28% decline in FEV₁. A confirmatory challenge was not conducted. In a larger study by Buckley et al, 134 patients underwent single-blind challenges with potassium metabisulfite capsules.¹⁸ Of these, 4.6% were reported to have sulfite sensitivity. In these three preliminary studies, the patient populations consisted of asthmatic subjects with corticosteroid dependency who were being evaluated at an allergy referral center. Thus, the prevalence, based on these observations, is probably not applicable to the asthma population as a whole, because corticosteroid dependency is one of the clinical characteristics of sulfite-sensitive asthmatic individuals.

In the largest study reported to date, Bush et al conducted capsule and neutral solution sulfite challenges in 203 adult asthmatic subjects.¹⁹ Subjects were not selected for a history of sulfite sensitivity. Of these individuals, 120 were not receiving corticosteroids, while 83 were corticosteroid dependent. Of the non-corticosteroid-dependent group, only 1 individual experienced a 20% or greater decline in FEV₁ values after single-blind and confirmatory double-blind challenges. The response rate in the corticosteroid-dependent asthmatic group was higher (8.4%). The prevalence in the asthmatic population as a whole was less than 3.9%, and corticosteroid-dependent asthmatic patients appeared to be most at risk for sulfite sensitivity.

Although corticosteroid-dependent asthmatic individuals have the

highest incidence of positive sulfite challenge results, they are not the only group at risk. In the history of sulfite-sensitive asthmatic patients, it is noteworthy that originally these individuals were not corticosteroid dependent or even asthmatic while undergoing their initial sulfite reactions. In fact, most did not have asthma when they began having severe restaurant-provoked bronchospastic reactions. Only later did they develop chronic asthma which became corticosteroid dependent. Therefore, the population at risk may include an early asthmatic or preasthmatic individual, indistinguishable from the general populace. Fortunately, based on studies and reports, the number of these patients is small.¹¹⁷

The incidence of sulfite sensitivity in the pediatric population is also unknown. As noted earlier, the first case of sulfite-induced bronchospasm was in a child.⁵⁴ Since then, there have been two other isolated case reports of alleged sulfite-sensitive children.^{109, 145} However, these reports did not include properly designed and blind challenges. Whether any of these three patients are, in fact, sulfite sensitive remains in question. In one study of chronic asthmatic children, almost two thirds were reported to be sulfite sensitive after open ingestion challenge.¹³⁶ Challenges did not include controls, and the children reacted only to large doses of sulfite solutions. These children may have reacted to the higher levels of sulfur dioxide generated in solution that was swallowed. Whatever the prevalence, investigators generally agree that sulfite reactions have decreased markedly since 1986 when the FDA banned the use of sulfites in fresh food and required labeling for other sources of sulfites.

Benzoates and Parabens

The next most commonly reported additives that might cause bronchospasm in patients with asthma are the parabens. In Freedman's³² study, 4 of 14 patients with a history of sensitivity to orange drinks had positive bronchospastic reactions to sodium benzoate in uncontrolled challenges. Maximum decreases in FEV₁ values ranged from 23% to 33% between 10 and 30 minutes after 20 to 100 mg of sodium benzoate. Samter and Beers,⁹⁶ as noted earlier for tartrazine, reported that sodium benzoate was a commonly used preservative in the foods that their ASA-sensitive patients reacted to by history. In Rosenhall's⁹² study, despite poorly designed challenges, only 1 of 504 patients reacted to a dose of sodium benzoate (<100 mg). Weber et al¹⁴² found only 1 of 43 patients with a positive reaction to 250 mg of sodium benzoate or hydroxy-benzoic acid in double-blind studies. Furthermore, when this patient was rechallenged 2 years later, he did not react to the same provoking dose of sodium benzoate.

The study of Genton et al³⁵ also examined asthmatic reactions to sodium benzoate and found only 1 of 17 subjects who was reported to have "reacted."

The only authors to report a double-blind, placebo-controlled, ben-

zoate-induced reaction are Tarlo and Broder.¹³¹ Once again, their patient was described as being ASA insensitive. Additionally, no improvement was noted in this patient's asthma when benzoate was removed from the diet.

MSG

The initial report of MSG-provoked asthma described two patients with delayed asthmatic reactions (12 hours postingestion)⁶; however, a subsequent report described four other patients with a history of CRS (and asthma in the fourth patient) experiencing a respiratory arrest within 3 hours of the Chinese meal.⁵ Open or single-blind challenges with changes in peak respiratory flow rates were used to confirm positive reactions. In addition, 3 of 12 asthmatic individuals without a history of Chinese restaurant-provoked asthma had positive challenges to MSG (all late). We have not seen a positive early or late reaction to MSG in our Scripps Clinic asthma population during double-blind, placebo-controlled challenges. One patient with a history suggestive of Chinese restaurant asthma had a positive reaction in a single-blind challenge. We have been unable to rechallenge this individual in a double-blind, placebo-controlled manner. A case describing MSG-provoked asthma has been reported. This individual had positive double-blind, placebo-controlled MSG and sulfite challenges.⁵⁹ Not surprisingly, there are two reports involving small numbers of mild asthmatic individuals, without a suggestive history, who were not found to react to MSG during oral challenges.^{37, 104}

BHA and BHT

In 1973, Fisherman and Cohen reported seven patients with either asthma or rhinitis who were said to be intolerant to BHA and BHT.³⁰ These patients were identified by a doubling of their earlobe bleeding times. Clinical details, or the reasons why BHA or BHT was ever suspected to cause difficulty were not given. The rationale for the reported effect on the bleeding time was not given. During the next year, while performing a similar study, Cloninger and Novey refuted these findings.³¹

Other Chemicals

Benzalkonium Chloride

Paradoxical responses to nebulized ipatropium bromide¹¹ and beclomethasone dipropionate²³ led to the discovery that the antibacterial preservative benzalkonium chloride causes bronchoconstriction in about

60% of asthmatic subjects. The characteristics of the responses—rapid onset with slow recovery over 60 minutes and inhibition by cromolyn but not ipatropium—suggest a mechanism of action via release of mediators.¹⁴⁷ The benzalkonium chloride concentration in commercial nebulizer solutions has been reduced so that only the rare patient with apparent immunological sensitivity will now react.⁸⁵

Spearmint

The flavors spearmint (*Mentha spicata*), peppermint (*Mentha piperita*), and menthol (*Mentha labiateae*), used in chewing gum and toothpaste, have been confirmed by challenges in two cases to have triggered asthma.^{123, 129}

Summary

Carefully designed, rigorously controlled studies have failed to confirm asthmatic reactions provided by tartrazine (or other azo and non-azo dyes). Sulfites, on the other hand, have clearly been shown to produce serious, even life-threatening, asthmatic reactions by several proposed mechanisms. Approximately 3% to 5% of asthmatic patients are sulfite sensitive, most of whom react by inhaling sulfur dioxide generated when sulfites are placed in solution. When the FDA banned the adding of sulfites to fresh foods in 1986, the frequency, and therefore importance, of this problem was greatly diminished. Benzoates and parabens have not been conclusively shown to be a significant problem for asthmatic individuals, even for those who are ASA sensitive. MSG may occasionally produce asthmatic reactions but certainly does not present a problem to the vast majority of asthmatic individuals. BHA and BHT have not been shown to produce asthmatic problems.

Benzalkonium chloride can frequently cause bronchoconstriction when inhaled by asthmatic subjects, but the concentration now used is so low that only individuals with immediate hypersensitivity will react; fortunately, such patients are rare. Recently, spearmint flavoring has been shown to trigger asthma in two cases.

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