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A M E R I C A N C O L L E G E O F



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# Precipitating Factors in Asthma\*

## Aspirin, Sulfites, and Other Drugs and Chemicals

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Several types of reactions to drugs and chemicals added to foods and drugs can precipitate asthmatic attack or perpetuate chronic asthmatic relapse. Anaphylactic reactions triggered by interaction of a drug—eg, penicillin—and IgE antibodies of the susceptible host, usually include a component of bronchospasm; the mechanisms of these reactions have been summarized in this symposium by Michael Kaliner and Robert Lewis. The pathophysiology of asthma includes a state of relative  $\beta_2$ -adrenergic blockade (see article by Warren S. Gold, this issue). Therefore, pharmacologic agents such as propranolol, used for their  $\beta_1$ -blocking action in the cardiovascular system but also possessing  $\beta_2$ -blocking action, can unmask a latent asthmatic potential or compound ongoing asthma, and therefore are best avoided in the asthmatic. This subject has been reviewed in depth in a conference sponsored by the American College of Chest Physicians.<sup>1</sup> The focus of this article is on the roles of aspirin and aspirin-like drugs and sulfites and other chemicals added to foods and drugs in precipitating or perpetuating asthmatic attack.

### ASPIRIN

Aspirin has been used for 75 years in the United States as

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an anti-inflammatory, antipyretic, and analgesic agent, and more recently as a platelet-inhibiting agent to prevent thrombotic and embolic disease. The average per capita consumption is more than 60 5-grain tablets per year. Asthmatic reaction to aspirin was first reported in 1911,<sup>2</sup> the intervening history of observations on idiosyncratic reactions to aspirin are summarized by VanArsdel.<sup>3</sup> Idiosyncratic reaction to aspirin may be manifest either by flare of respiratory disease or urticaria-angioedema; only very few individuals have been reported to have both respiratory and cutaneous response to aspirin.

The typical aspirin-sensitive respiratory syndrome primarily affects adults,<sup>4</sup> though onset may be in childhood.<sup>5</sup> The disease evolves over decades and ordinarily begins with a perennial vasomotor-irritant aggravated type of rhinitis, though a third of these patients also have IgE-mediated cutaneous reactions to aeroallergen extracts. Next an eosinophilic hyperplastic rhinosinusitis with nasal polyps ensues, and, not infrequently, this is complicated by bouts of purulent bacterial sinusitis. Intrinsic asthma then appears and progresses to require treatment with systemic steroids. The earmark of aspirin sensitivity is the appearance of facial or generalized flush, ocular and nasal congestion, and acute, often severe, asthmatic attack within one half to several hours after ingesting an ordinary dose of aspirin or aspirin-like drug. Even though the patient soon learns to avoid aspirin and similar drugs, the underlying respiratory disease continues.

The prevalence of aspirin sensitivity in patients with asthma varies according to the population studied and methods used to detect the sensitivity. Giraldo et al<sup>6</sup> found 3 to 5 percent of hospitalized asthmatic patients had a history of reaction to aspirin. At Scripps Clinic, a secondary and tertiary medical center, we found that about 10 percent of our asthmatic population was aspirin-sensitive.<sup>4</sup> At the National Jewish Hospital, where an even more highly selected group of severely asthmatic patients were studied, 19 percent were found by oral challenges to have idiosyncratic reaction to aspirin.<sup>7</sup> Among asthmatic patients with pansinusitis and nasal polyps, 30 to 40 percent are aspirin sensitive.<sup>8</sup>

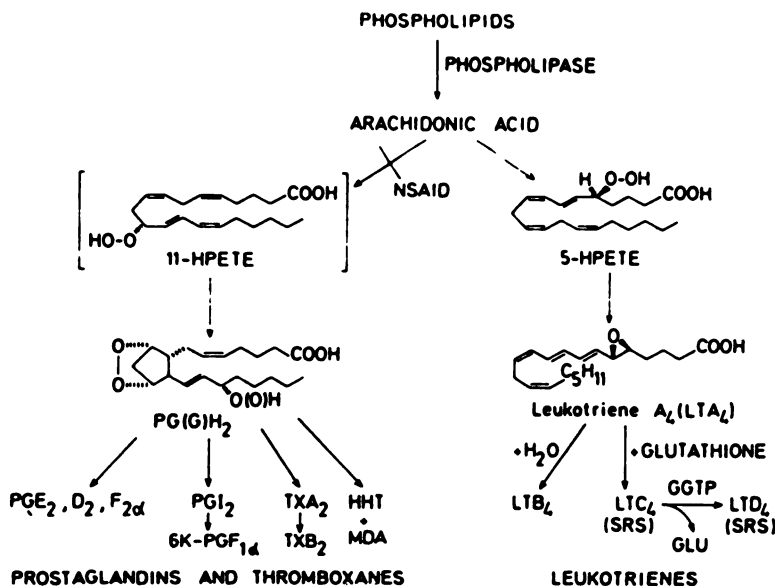


FIGURE 1. Phospholipid-arachidonate metabolic pathways of probable relevance to aspirin sensitivity in respiratory diseases. Nonsteroidal anti-inflammatory drugs (NSAID) block cyclooxygenase pathways.

**Table 1—Cross-sensitivity between Aspirin and Other Nonsteroidal Anti-inflammatory Drugs**

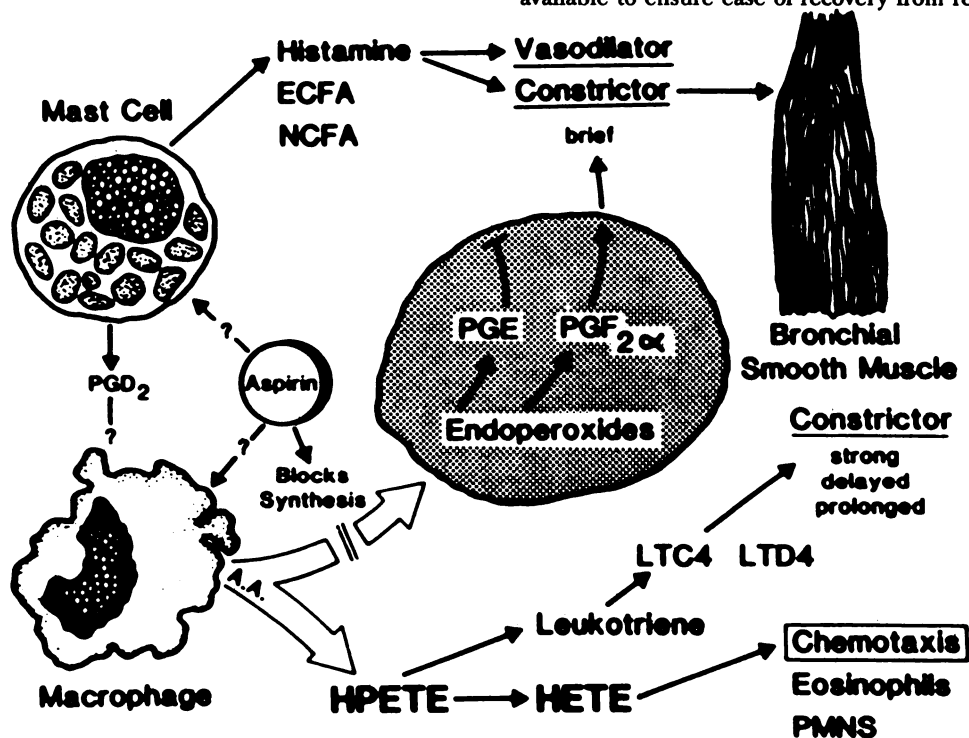
Cyclooxygenase Inhibition	Prevalence of Cross-sensitivity with Aspirin
<b>Inhibitors</b>	High, >90%
Indomethacin (Indocin)	
Fenoprofen (Nalfon)	
Naproxen (Naprosyn, Anaprox)	
Ibuprofen (Motrin, Brufen)	
Mefenamic acid (Ponstel)	
Sulindac (Clinoril)	
Meclofenamate (Meclomen)	
<b>Partial inhibitors</b>	Occasional
Oxyphenbutazone (Oxalid, Tandearil)	
Phenylbutazone (Butazolidin)	Isolated case reports
<b>Noninhibitors</b>	
Sodium salicylate	
Choline salicylate	
Salicylamide	
Propoxyphene Acetaminophen	

The Nobel Prize in Medicine in 1982 was awarded to Dr. John Vane, Dr. Bengt Samuelsson, and Dr. Sune Bergström for their studies of metabolites of arachidonic acid (Fig 1). Dr. Vane identified a mechanism of action of aspirin to be the inhibition of prostaglandin synthesis from the cyclooxygenase pathway of arachidonate metabolism. Other nonsteroidal anti-inflammatory drugs which inhibit this pathway also can provoke a respiratory reaction in aspirin-sensitive asthmatic subjects. As shown in Table 1, cross-sensitivity correlates with the effectiveness of cyclooxygenase inhibition.

When we studied 50 consecutive asthmatic patients who had a history of aspirin sensitivity by cautious oral challenges with aspirin, we found a spectrum of reactions.<sup>9</sup> The majority of these patients experienced a typical ocular, nasal, and asthmatic response; however, 12 percent had a nasal-ocular response without definite asthmatic reaction, and 16 percent had no adverse reaction whatsoever. Further, in several patients in whom we repeated the aspirin challenges, there was variation of an individual's response, including one patient challenged on 4 occasions over a 9-year interval who had typical ocular, nasal, and asthmatic reactions following the first 2 challenges, no reaction following the 3rd, and only a nasal response following the 4th.

As aspirin sensitivity may occur in up to 15% of asthmatic patients, but appear only after years of progression of the respiratory disorder and vary in its expression and since the vast majority of asthmatic patients can avoid aspirin and aspirin-like drugs, the prudent approach to all asthmatic patients is to advise them to avoid these drugs by substituting acetaminophen. For the occasional patient with aspirin-sensitive respiratory disease who also has vascular disease requiring an inhibitor of platelet aggregation-embolization or musculo-rheumatic disease that is inadequately responsive to nonaspirin-like drugs, desensitization with oral challenges with incremental doses of aspirin or aspirin-like drugs, followed by at least daily administration of the drug, can be accomplished.<sup>10</sup>

Challenges-desensitizations must be performed using a number of safety practices. At Scripps Clinic, we perform challenges within the hospital, where emergency resuscitative equipment, an intensive care unit, and trained personnel are readily available; challenges are always started in the morning so that optimal time and treatment are available to ensure ease of recovery from reaction; patients



**FIGURE 2.** Cellular and mediator pathways affecting bronchoconstriction and inflammation which may be of relevance to aspirin sensitivity in respiratory diseases (details in text).

are challenged at a time when their asthma is in remission; if need be, we administer additional corticosteroid for several days prior to challenge to ensure that there is full remission; and, to proceed with the challenge, the patient must have a one-second forced expiratory volume (FEV<sub>1</sub>) greater than 70 percent of predicted or his best previously recorded, and, in absolute numbers, this must be greater than 1.5 L. We observe our patients for not only asthmatic, but also ocular and nasal responses.

Asthmatic patients who have a history of having had severe reaction to aspirin are challenged-desensitized over at least a 2-day interval with aspirin given at 3-hour intervals, beginning with a dose of 3 mg and then 30, 60, and 100 mg, and then, on the 2nd day, 150, 325, and 650 mg of aspirin. For patients who do not have a history of aspirin sensitivity, but also have not taken aspirin in recent months, a 1-day challenge with doses of 30, 60, 100, 325, and 650 mg at 2-hour intervals can be initiated. For any patient, if there is a fall of FEV<sub>1</sub> greater than 25 percent from baseline, the challenge is suspended, treatments with inhalations of sympathomimetic and additional doses of corticosteroid and aminophylline are administered; and the challenge is resumed the following morning (if criteria are met), beginning with the dose which provoked reaction on the previous day. Up to 8 or more provoked asthmatic attacks may be required before a desensitized state is achieved.

Sensitization may recur from 1 to 5 days after interruption of therapy; for this reason, it is imperative that the patient continue taking the aspirin or aspirin-like drug on a daily basis if continuous desensitization is the objective.

We followed-up 2 patients who had undergone aspirin desensitization and continued taking daily aspirin treatment, and we found them to have improvement in their respiratory disease and less need for steroid treatment.<sup>11</sup> We subsequently studied the efficacy of treatment with aspirin in 25 aspirin-sensitive asthmatic patients in a 7-month, randomized, placebo-controlled, double-blind, crossover trial.<sup>12</sup> A significant improvement in rhinosinusitis occurred in about 2/3 of the patients during aspirin maintenance compared with the placebo, and a majority of the patients had improvement in their asthma, though not reaching statistical significance. A few of the patients had even greater respiratory symptoms while taking aspirin compared to the placebo. We continue investigative studies aimed at better identifying those subsets of aspirin-sensitive patients who might benefit from this treatment.

The mechanism(s) underlying sensitivity to aspirin has not been identified. The sites at which aspirin might act to influence the generation of mediators implicated in the asthmatic response are shown in Figure 2. Thus far, there have been mostly negative results from tests of hypotheses for aspirin sensitivity. IgE antibodies or other immunologic response to aspirin have not been identified. There does not appear to be an imbalance of the bronchodilating prostaglandin E<sub>2</sub> or bronchoconstricting PGF<sub>2α</sub> following aspirin ingestion. Benoxaprofen, a nonsteroidal anti-inflammatory drug which may inhibit the lipoygenase pathway of arachidonate metabolism, does not block the aspirin reaction.<sup>13</sup> Mast cell mediator (histamine, neutrophil chemotactic factor), activation of complement, and release of platelet factor 4 have not been measured in association with the aspirin-sensitive

response.<sup>14,15</sup> There may be activation of the contact-kinin system as evidenced by endogenous heparin release, reduced *in vitro* bradykinin releasable high molecular weight kininogen, and enhanced *in vitro* stimulated appearance of kallikrein.<sup>16</sup>

#### SULFITES—SULFUR DIOXIDE

Sulfur dioxide and a variety of sulfiting agents, including potassium metabisulfite (K<sub>2</sub>S<sub>2</sub>O<sub>5</sub>), have been used for centuries as preservatives, sanitizing agents for food containers, selective inhibitors of growth of microorganisms in the fermentation industries, and as inhibitors of enzyme-catalyzed oxidative discoloration and nonenzyme browning during the preparation, distribution, and storage of foods. Because ingestion of sulfites, even in large amounts, does not have apparent ill effect in normal individuals, these agents appear on the United States Food and Drug Administration (FDA) "Generally Recognized As Safe" (GRAS) list and therefore may be added to nonthiamine (sulfites destroy thiamine)-containing foods and drinks without disclosure.

Information on the commercial use of sulfites is incomplete. Table 2 lists foods and beverages commonly preserved with sulfur dioxide gas or a solution or powder of K<sub>2</sub>S<sub>2</sub>O<sub>5</sub> or other sulfite. The estimated consumption of sulfites in US diets is 2 to 3 mg/day in the home, 5 to 10 mg/oz of beer or wine consumed, and 25 to 200 mg/restaurant meal.

Initial reports of reactions to ingested sulfites were of anaphylactoid reactions, including urticaria-angioedema.<sup>17,18</sup> Although the evidence presented in these reports is equivocal, there is the suggestion that these reactions may have been IgE mediated, or at least associated with mast cell mediators of anaphylaxis.

Sulfites in solution, especially at the acid pH of saliva or gastric juice, will generate sulfur dioxide. Sulfur dioxide, a common air pollutant, at a concentration of 0.50 parts per million (ppm; within the range commonly experienced in air pollution episodes) induces bronchoconstriction in asthmatic subjects during exercise.<sup>19</sup> Reactivity to inhaled sulfur dioxide in asthmatic patients likely correlates with the degree of underlying airway hyperreactivity—degree of asthmatic potential.

Within the past 7 years, we and others have reported the cases of asthmatic patients who have experienced acute severe choking asthmatic distress within minutes of ingesting sulfites.<sup>20-22</sup> These patients had asthmatic response to as little as 5 mg of ingested sulfite. We have found several of our patients to have fibroblast sulfite oxidase (the enzyme which catalyzes oxidation of sulfites to sulfates) levels intermediate between those reported for homozygous deficiency for this

**Table 2—Foods and Beverages Commonly Preserved With Sulfur Dioxide and/or Sulfites**

Dried and packaged fruits and beverages
Beers, wines, and other fermented beverages
Salads, including all ingredients (salad bars)
Avocado—guacamole and other dips
Potatoes—chips, fries, dehydrated
Cider and wine vinegars—pickled vegetables
Shrimp and other seafoods
Processed, preserved, "ready to eat" foods and beverages

enzyme and normal levels;<sup>23</sup> this deficiency may account for the exquisite sensitivity to sulfite in these patients.

Delohery et al<sup>24</sup> described several asthmatic patients in whom oral (mouthwash) but not gastrointestinal administration of sulfites precipitated an asthma attack; they raised the possibility that oral-tracheobronchial reflexes might account for this response.

Sulfites are also used as antioxidants in the pharmaceutical industry. Asthmatic reactions with inhalation of isoetharine (Bronkosol)<sup>25</sup> and sulfite solution at the concentration found in isoproterenol (Isuprel),<sup>26</sup> and injections of metochlopramide (Reglan)<sup>25</sup> have been reported. The reactions to the inhaled sulfites may be mediated by SO<sub>2</sub>; concentrations of 1 ppm SO<sub>2</sub> appear with inhalations of the solutions reported to provoke asthmatic response. The concentration of sulfites in solution of multidose vials of metaproterenol (Alupent) is less likely to provoke reaction.<sup>27</sup> Sulfites are not found in unit-dose metaproterenol (Alupent), metered-dose canisters of bronchodilators, or terbutaline solution. We have not provoked asthmatic reaction in our exquisitely sulfite sensitive asthmatic patients with subcutaneous injections of sulfites in the concentration doses commonly administered with aqueous epinephrine.<sup>28</sup>

We estimate the prevalence of sensitivities to sulfites, be they anaphylactic/oid, sulfite oxidase deficient, oral-tracheobronchial reflex, and/or bronchial hyperreactivity to inhaled SO<sub>2</sub>, to be of clinical consequence in at least 5 percent if not 10 percent or more of asthmatic patients. For practical purposes, in those asthmatic patients in whom the history suggests that sulfite or SO<sub>2</sub> may be a precipitator or perpetuator of asthmatic relapse (attack with ingestion of fermented beverages or restaurant meals or with exercise during periods of aeropollution), we perform cautious challenges with sulfites.

Patients are challenged at a time when their asthma is in remission as documented by FEV<sub>1</sub> of greater than 70 percent of predicted and at least 1.5 L absolute. Inhaled cromolyn, antihistamines, and bronchodilator medications are withheld on the day of challenge; other medications are continued. Open oral challenges are administered with doses of 1, 5, 10, 25, 50, 100, and 200 mg in freshly prepared lemon juice taken by mouth/sublingual swishing and swallowing at 15-minute intervals. Spirometric measurements are performed at ten-minute intervals throughout and challenge suspended if there is fall of FEV<sub>1</sub> of 25 percent or more. Airways obstruction is reversed with inhalations of metaproterenol. Apparent reaction is verified with double-blinded, placebo-controlled challenges.

Those patients who have been identified to be sensitive to sulfites are counseled in the avoidance of sulfites added to foods and drugs and are invited to participate in investigative studies aimed at better understanding the phenomenon. These studies include studies of blocking the reaction with cromolyn, antihistamine, atropine, and cyanocobalamin (vitamin B<sub>12</sub>), a nonspecific catalyst of oxidation, and cutaneous biopsies for fibroblast cultures-sulfite oxidase assays.<sup>23,29</sup>

#### OTHER CHEMICALS

Tartrazine (FDA Yellow No. 5), a coal tar-derived food and drug azo dye, has been reported to provoke asthmatic reaction by several authors; however, virtually all of the

reports do not include blinded and placebo-controlled challenges.<sup>30</sup> At Scripps Clinic we have performed blinded-controlled challenges with tartrazine in doses up to 75 mg by mouth in over 100 aspirin-sensitive asthmatic patients and have yet to identify a single patient sensitive to tartrazine.

Likewise, though concern has been raised through reports of cases of asthma apparently aggravated by ingestion of monosodium glutamate, sodium benzoate, parahydroxybenzoic acid, parabens, other azo and non-azo dyes (amaranth, ponceau, sunset yellow, brilliant blue, erythrosine, and indigotin), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), or potassium sorbate, blinded, controlled challenges with these agents have generally not confirmed presence of such sensitivities in large populations of asthmatic patients.<sup>31,32</sup>

#### SUMMARY

Several types of reactions to drugs and chemicals may precipitate or perpetuate asthmatic relapse. This review focuses on reactions to aspirin and sulfites. Approximately 40 percent of patients with rhinosinusitis, nasal polyps, and asthma and 5 to 10 percent of all asthmatic patients are sensitive to aspirin and aspirin-like nonsteroidal anti-inflammatory drugs at some time in their course. A prudent recommendation to all asthmatics is to substitute acetaminophen for aspirin. When aspirin/aspirin-like drug is essential for treatment of cardiovascular or musculoskeletal disorder, desensitization by cautious oral challenges with graded doses of aspirin can be accomplished. Treatment of the respiratory disorder per se by desensitization followed by daily therapeutic aspirin remains investigational. Sulfur dioxide and sulfites, commonly used as sanitizers and preservatives of foods and pharmaceuticals, may precipitate acute asthma in 5 percent or more of asthmatic patients. When the history suggests sulfite sensitivity, challenges can be used to confirm sensitivity and the patient counseled in avoidance of these chemicals.

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