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Samter M & Beers R F, Jr. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann. Intern. Med.* 68:975-83, 1968.
[University of Illinois, College of Medicine, Chicago, IL]

Polyps and bronchial asthma, caused by reactions to aspirin, are rare in childhood. Most patients become "aspirin sensitive" in middle age; respiratory symptoms precede the development of intolerance to aspirin. Salicylates other than acetylsalicylic acid are innocuous, but nonsteroidal anti-inflammatory compounds may act like aspirin. Tartrazine—a food color, not an analgesic—causes occasional reactions, but the reason is still a matter of speculation. [The *SCI*® indicates that this paper has been cited in over 280 publications.]

Max Samter
Max Samter Institute of Allergy
and Clinical Immunology
Grant Hospital of Chicago
Chicago, IL 60614

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When we became interested in "idiosyncrasy" to aspirin, reactions to aspirin had been known for 50 years. Allergy had not yet emerged from its preoccupation with "haptens"—small chemicals attached to macromolecular carriers and capable of inducing hapten-specific immunological reactions. Several publications classified salicylates as haptens; one paper went so far as to demonstrate antibodies to aspirin, but this has never been confirmed. In fact, we learned with some surprise that most of our original patients were nonatopic. Yet the *Annals* returned our manuscript several times with elaborate comments of referees who insisted that reactions to aspirin must be allergic reactions. When the paper was finally accepted, the acceptance came with a note from the editor, who complimented us on our decision not to give up.

Meanwhile, Stevenson and his associates—extending a chance observation by Roy Patterson and his group—found that it is possible to "desensitize" patients to aspirin, but only when therapeutic levels are reached and maintained.[1] If interrupted, the intolerance recurs, and the underlying disease does not change.

Much has happened since then. It became clear, for instance, that some aspirin-sensitive patients not only reacted to aspirin but also to nonsteroidal anti-inflammatory drugs (NSAIDs) and other substances (including the food color FD&C Yellow No. 5 [tartrazine], a pyrazolone derivative). It seemed tempting to believe that the prostaglandin system must be involved.[2]

However, our own chapter on the subject in the last edition of *Immunological Diseases*, called "The Aspirin Triad and the Prostaglandins,"[3] suggested that the prostaglandin system might have nothing to do with intolerance to aspirin. In general, the reasoning was ingenious: aspirin and NSAIDs block cyclo-oxygenase, which transforms arachidonic acid into thromboxanes and prostaglandins. If cyclo-oxygenase is blocked, the lipoxygenase can take over and transform arachidonic acid into leukotrienes, which act strongly on the respiratory tract. If this explanation holds, it would be a miracle that only a small fraction of asthmatic patients is aspirin-sensitive.

As far as FD&C No. 5 is concerned, not much progress has been made: it is still not clear whether a metabolite or a contaminant is responsible for the reactions. Surprisingly, Stevenson has used the same tartrazine that we have used and has been unable to induce a single reaction;[4] this is a riddle to both of us. We suspect that the attention that has been paid to our original publication suggests: (1) that bronchial asthma is still an enigmatic disease and (2) that there is hope that reactions to aspirin will turn out to be a new breed of biological defect that will eventually make us understand bronchial asthma better than we do now.

1. **Pleskow W W, Stevenson D D, Mathison D A, Simon R A, Schatz M & Zeiger R S.** Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J. Allerg. Clin. Immunol.* 69:11-19, 1982.
2. **Szczeklik A, Gryglewski R J & Czerniawska-Mysik G.** Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *Brit. Med. J.* 1:67-9, 1975. (Cited 145 times.)
3. **Zeitz H J & Jarmoszuk I J.** Nasal polyps, bronchial asthma, and the aspirin sensitivity: the Samter Syndrome. *Compr. Ther.* 11:21-6, 1985.
4. **Stevenson D D, Simon R A, Lumry W R & Mathison D A.** Adverse reactions to tartrazine. *J. Allerg. Clin. Immunol.* 1986. (In press.)