Aspirin-Sensitive Asthma*

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Aspirin intolerance is particularly common in asthmatic patients who additionally have chronic rhinitis and/or nasal polyps. These individuals differ in several respects from patients who experience urticaria and/or angioedema after aspirin administration, and differing mechanisms may be involved. Data regarding the latter are indirect and incomplete, but suggest that ASA-sensitive asthma is most likely to be related in some manner to the capacity of ASA to inhibit cyclooxygenases, enhanced lipoxynase metabolism perhaps playing a crucial role. Current research employing ASA "desensitization" may help to elucidate these enigmas.

Adverse—even fatal—reactions to aspirin (ASA) ingestion have been known to occur in “sensitive” individuals since the early 1900s. These reactions, occurring 20 minutes to three hours after ingestion,1 usually present as primarily: 1) a respiratory pattern dominated by bronchospasm, rhinorrhea, conjunctivitis and/or flushing; 2) by an urticaria/angioedema response; or 3) rarely as a combination of these patterns.1

While ASA sensitivity occurs among a few apparently healthy persons2 and chronic rhinitis patients,2 it is much more common among those with asthma2 and/or nasal polyps. Although occurring in children,3 the frequency of this pattern increases with age4 and is typically of the mixed respiratory type.5,6,7 Asthmatic patients with nasal polyps and aspirin sensitivity commonly are referred to as triad asthmatics. However, provocation of nasal symptoms may be the sole manifestation of sensitivity in a subgroup of nonasthmatic subjects with rhinosinusitis and tendency towards polyps.8 Among asthmatic patients with a history of aspirin intolerance, oral ASA challenge has resulted in both an asthmatic and naso-ocular response in 66 percent of 50 subjects, purely an asthmatic response in 6 percent, purely a naso-ocular response in 6 percent, and no response in 16 percent.7 Asthmatic responses also can be induced through administering ASA by aerosol.8 Spontaneous remission of ASA sensitivity has been documented in a few cases by repeated challenge with ASA after several years.7

Estimates of the prevalence of ASA sensitivity are enormously variable, ranging from 0.9 percent in normal subjects2 to 78 percent in a selected population of severe asthmatic patients with nasal polyps.9 Within this spectrum it has been reported in 1.4 percent of chronic rhinitis patients,10 14-22 percent of persons with nasal polyps10 and 3.8-28 percent of asthmatic patients in general.2,11 Part of this variability can be attributed to varying criteria for this diagnosis, such as history alone vs challenge testing, and the lack of standardization of challenge tests. The urticarial response, common in chronic urticaria patients, more likely has a different pathogenesis (perhaps occasionally IgE mediated) than does the respiratory reaction which is the subject of this discussion.

Clinical features of ASA sensitivity10 are shown in Table 1. Longstanding vasomotor rhinitis and severe intrinsic asthma often precede ASA sensitivity.1,2,4 Nasal polyposis and usually the asthma persist despite avoidance of aspirin.11 Although a familial clustering of asthma, rhinitis and ASA sensitivity has been seen,12 there was discordance of ASA sensitivity in the two monozygotic twin pairs reported,4,12 as well as documented improvement in asthma after ASA in a sibling of an ASA-sensitive proband in another kindred.12 In a study of a small number of patients, HLA A1/B8 was preponderant, but this haplotype may be increased in asthma per se.13

Mechanism

An immunologic process initially was assumed to explain ASA sensitivity. Indeed, the ASA-induced asthma/rhinoconjunctivitis symptom complex often does resemble an anaphylactoid reaction. However, an
Occasional cross reactivity with other NSAI derivates, specific peripheral eosinophilia, vaso~notor  

An exception may be urticarial responders in whom  

Nasal polyposis and/or  

Mediation by cyclooxygenase and/or lipoxygenase products  

immmunologic basis for ASA sensitive asthma is doubtful since studies of immediate skin tests with aspiril derivate, passive transfer of sensitivity to humans or monkeys, IgE specific anti-aspiril antibodies, lymphocyte proliferation, polypl immunofluorescence, and hemagglutinating antibodies all have been negative or have failed to correlate with clinical sensitivity. An exception may be urticarial responders in whom positive skin tests occasionally have been seen.  

The role of mast cell or basophil-derived mediators and complement activation has received attention with equivocal results. Although increases in venous whole blood and plasma histamine have been reported in ASA-induced asthma, other reports indicate no change from baseline in arterial and venous plasma or urinary histamine (H) or neutrophil chemotactic activity during reactions. In addition, in some asthmatic patients an increase in plasma H was not accompanied by a clinical reaction. Finally, ability to assess plasma H is plagued by the problem of rapid metabolism in vitro and of unreliability of various assay techniques. Other studies of the role of mediator release using cromolyn as a potential inhibitor of the clinical response have also given conflicting results: in some instances there was a delay in the fall of FEV₁, while in others no effect on the reaction onset or magnitude was observed. In a study in which the antihistamine clemastine appeared to block the ASA reaction in some patients, the mere five-day interval between the successive ASA challenges did not rule out partial desensitization by the previous reaction. The recently reported protective effect of ketotifen might be due either to this drug's mast cell-stabilizing effect or to its antihistamine properties.  

Although ingestion of ASA in sensitive asthmatic patients has been reported to produce a fall in plasma complement, in some patients this occurs after salicylate ingestion in the absence of an asthmatic response. In addition, ASA and salicylate produced similar declines in serum complement and Cl esterase inhibitor in vitro and in vivo in normal subjects and in nonsensitive asthmatic patients. Confirming our own experience with five triad asthmatic patients, anaphylatoxin inactivator (serum carboxypeptidase N) has been reported to be present in normal amounts in ASA-intolerant persons. Finally, others have observed no change in arterial or venous plasma CH₅0₂, C₄, or C4d chemotactic activity during positive ASA challenges. A possible intermediary role for a cholinergic mechanism in ASA-induced asthma has been considered, but methacholine bronchial challenge was still positive in two patients "desensitized" to aspirin (although it was not stated whether a change in threshold occurred). We have observed no change in threshold reactivity to inhaled methacholine in three patients following ASA desensitization. Possible involvement of the contact system requires further investigation.  

It seems most likely that ASA-induced asthma in some way is secondary to this drug's effects on arachidonic acid metabolism. As is well known, this cell membrane fatty acid can be metabolized along two pathways (Fig 1): (1) via cyclooxygenase to unstable endoperoxides which are subsequently converted in various proportions to prostaglandins (PGs), thromboxanes (TX), and prostacyclin, depending on tissue type and stimulus, and (2) via lipoxygenase peroxidation to hydroperoxyeicosatetraenoic acids (HPETEs) which are precursors in the formation of hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs). The latter include LTC₄, LTD₄, and LTE₄, which comprise the classic slow-reacting substance of anaphylaxis (SRS-A) that is released during anaphylaxis and by other stimuli. Both the physiologic and pharmacologic effects of the cyclooxygenase and lipoxygenase derivatives are complex, varying with species, stimulus, cell source, and target cells among other factors. Regarding PGs in man, those of the F, A, B, and D₄ series and TXB₂ are bronchoconstrictors, while E series PGs and PGL₁ bronchodilate. The bronchoconstrictor effect of PGF₂α appears to be mediated through cholinergic mechanisms. Not only are cyclooxygenase products released during anaphylaxis, but specifically the PGF₂α metabolite has been reported to be released in allergen-induced asthma. In addition, the PGs themselves affect mediator release; for example, PGE blocks antigen-induced histamine and SRS-A release from sensitized human lung and histamine release from basrophils, while PGF₂α enhances antigen induced mediator release. These effects probably are mediated through altered intracellular cyclic nucleotide levels. ASA and other cyclooxygenase inhibitors enhance antigen-induced release of SRS-A from lung and of histamine from lung and basrophils.  

Some properties of the lipoxygenase metabolites in-

Table 1—Characteristics of ASA Sensitivity

<table>
<thead>
<tr>
<th>Type of Reaction</th>
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<tr>
<td>Feature</td>
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<tr>
<td>Vaso~notor rhinitis</td>
</tr>
<tr>
<td>Nasal polyposis (%)</td>
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<tr>
<td>Increased prevalence with age</td>
</tr>
<tr>
<td>Cross reactivity with other NSAI</td>
</tr>
<tr>
<td>Occasional familial clustering</td>
</tr>
<tr>
<td>Positive immediate skin tests to common aeroallergens</td>
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<tr>
<td>↑ serum IgE</td>
</tr>
<tr>
<td>Peripheral eosinophilia</td>
</tr>
<tr>
<td>Nasal eosinophilia</td>
</tr>
<tr>
<td>Specific IgE</td>
</tr>
<tr>
<td>Mediation by cyclooxygenase and/or lipoxygenase products</td>
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dicate a probable pathogenetic role in asthma. Most notable in this respect is the fact that LTs are powerful bronchoconstrictors—LTC\(_4\) and LTD\(_4\), having 1,000 times the potency of histamine on a molar basis.\(^8\) In addition, these lipoxigenase products have the potential to produce impaired mucociliary clearance,\(^9\) increased mucus production\(^9\) and mucosal edema/infiltration. This occurs from shunting of arachidonic acid metabolism into the 5-lipoxygenase pathway. In addition, there is evidence that 5-HPETE, and 5-HETE enhance histamine release.\(^10\) Other evidence suggesting that ASA sensitivity may be secondary to the capacity of ASA to block PG synthesis is as follows: 1) there is a 60 to 100 percent incidence of cross-sensitivity to aspirin by various structurally dissimilar cyclooxygenase inhibiting nonsteroidal antiinflammatory agents (NSAI),\(^3\) while sodium salicylate, a structurally similar agent with little capacity to inhibit PG synthesis, is usually well tolerated.\(^11\) 2) desensitization to ASA produces desensitization to other NSAI and vice versa;\(^2\) 3) the potency of PG synthesis inhibition in vitro correlates with its in vivo potency in producing bronchospasms in sensitive asthmatics;\(^3\) 4) in the rare instances in which ASA ingestion has been reported to improve asthma, other NSAI also had beneficial effects, while neither sodium salicylate nor salicylamide had a significant effect.\(^4\) A possible weakness in this aspect of the hypothesis is the alleged cross-sensitivity of a few aspirin-sensitive patients to tartrazine,\(^4\) as well as reported but less frequent cross-reactivity to Na benzoate\(^4\) and acetaminophen, none of which is known to inhibit PG synthesis.\(^5\) However, neither tartrazine nor Na benzoate cross-reactivity was demonstrable in double-blind challenges by other investigators.\(^6\)

Given the potential of both cyclooxygenase and lipoxigenase products to mediate an asthmatic reaction, there are several possible ways to explain ASA sensitivity within the framework of the PG inhibition hypothesis including: a) a change in the relative ratio of bronchoconstricting to bronchodilating and mediator releasing/inhibiting PGs; b) increased sensitivity to the bronchoconstricting effects of PGs; and c) a shift to the lipoxigenase pathway. The first postulate is not borne out experimentally since both baseline and post-ASA or piroxicam decreases in plasma or serum (mostly platelet derived) PGE\(_2\), PGF\(_{2\alpha}\), and TXB\(_2\) were the same in asthma reactors as nonreactors.\(^7\) It seems there was no evidence of a shift toward a less favorable ratio of bronchoconstricting to bronchodilating PGs and TXs.\(^8\) Also, both PGE\(_2\) and PFK\(_{2\alpha}\) were found to be elevated in a nasal polyp homogenate of an ASA-intolerant asthmatic.\(^9\) However, the as yet unconfirmed finding of greater inhibition by ASA of arachidonic acid stimulated production of PGE\(_2\)-like substances from nasal polyp homogenate or intact nasal polyps from ASA sensitive compared to nonsensitive polypectomy patients suggests that there may be tissue-specific (or target-organ specific) differences in sensitivity to ASA.\(^10\)

Sensitivity to PGs themselves appears the same in ASA-sensitive asthmatic patients as nonreactors since the former are: 1) not more sensitive to bronchoconstrictive PGs and may even have more bronchodilation than other asthmatic patients to the same dose of PGE\(_2\), and 2) they have the same increase in lymphocyte cAMP and beta-adrenergic receptor number and
function after PGE. Thus, it seems attractive to postulate that the shift to the lipoxygenase pathway is playing some role, which remains to be defined, in ASA-sensitive asthma. However, arguing against this hypothesis was the failure of oral benoxaprofen to raise the threshold or delay the onset of a clinical reaction in ASA-sensitive patients in spite of in vitro inhibition of SRS release. Thus, the lipoxygenase shift hypothesis is attractive, but as yet the release of SRS-A in blood or target issues during ASA-induced asthma has not been demonstrated.

ASA Desensitization

The possibility that patients could be desensitized to aspirin was suggested by the serendipitous finding of a 72-hour period of refractoriness to further aspirin-induced symptoms after the respiratory reaction to an initial dose of aspirin. This led to systematic desensitization of patients by the oral route, or by inhalation. For example, Pleskow et al administered serially increasing oral doses of aspirin (3, 30, 60, 100, 150, 300 mg) given at one- to three-hour intervals until at least a 25 percent fall in FEV, was elicited. Even with gradually increasing doses, the elicited reactions may include very severe asthma, rhinitis, and conjunctivitis requiring very close monitoring in an intensive care unit or its equivalent. Following treatment of the reaction with isoetharine and return of FEV, to near baseline (usually within two to 24 hours), aspirin was readministered in a dose equal to the last dose given just prior to the reaction and was incrementally increased until 650 mg of aspirin was tolerated without symptoms or a significant decrease in FEV, Such patients were defined as being “desensitized.” Doses and dose intervals were individualized if a reaction reappeared. The number of reactions required before desensitization was achieved correlated inversely with the cumulative dose required to provoke the initial reaction and was as high as six reactions, ie, seven of 11 patients reacting to a cumulative ASA dose of 150 mg or less experienced more than one reaction before becoming desensitized, three of 12 reacting at 280-450 mg had more than one reaction, and none of seven reacting at 500 mg or more experienced this type of problem. Two of our patients experienced five reactions before becoming desensitized. Following desensitization, patients are nonreactive to ASA for an average of two to four days with a range of 1-30 days. The desensitized state usually can be maintained virtually indefinitely by daily oral ASA, but one case has been reported of relapse after six months of successful aspirin desensitization (while receiving propranolol).

In our own experience, as with that of published series, patients usually tolerate substantial, therapeutic doses of ASA after “desensitization.” Cross desensitization to other NSAIs (eg, indomethacin) occurs after ASA desensitization, and, conversely, desensitization to ASA develops after a reaction to other NSAIs.

An initial report suggested overall clinical improvement in asthma of desensitized patients who continued to take daily aspirin, but this remains to be confirmed by further controlled studies (Table 2). One difficulty has been that these reports often have been based on subjective criteria or semiquantitative parameters not easily subject to statistical analysis. Even in the more successful trials, a significant portion of patients had worsening of symptoms which often required discontinuation of ASA. Rhinosinusitis symptoms improved more consistently than FEV, an observation which is in accord with our experience. Responses did not correlate with the maintenance dose of ASA used nor other variables studied. Finally, daily ASA had no effect on asthma severity in ten children with moderately severe, non-aspirin sensitive asthma.

To date, the mechanism of desensitization has not been elucidated. Some possibilities include: 1) depletion of mediators by ASA-induced reactions; 2) saturation of sites responsive to aspirin thereby preventing further release of mediators by aspirin; 3) tachyphylaxis to mediators; 4) increased clearance and/or degradation of mediators (eg, the induction of histaminase); 5) release of mediators during an initial reaction causing feedback inhibition of further mediator release; or 6) there may be a decrease in nonspecific airway irritability. Our preliminary studies have shown essentially no change in threshold for positive codeine (a nonspecific histamine liberator) and Aeroallergen immediate skin test reactions after ASA desensitization. Likewise, responses to bronchial challenge with Aeroallergens are not significantly altered. These observations argue against mediator depletion being responsible for ASA desensitization. A similar deduction might be made from the reported ability of ketotifen, an inhibitor of mast cell degranulation, to block ASA-induced reaction in a triad asthmatic but yet not prevent desensitization. Although conclusions

### Table 2—ASA Desensitization as Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Asthma</th>
<th>Rhinitis</th>
<th>Both</th>
<th>ASA Dose mg/24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevenson et al</td>
<td>25</td>
<td>44</td>
<td>56</td>
<td>32</td>
<td>325-2,600</td>
</tr>
<tr>
<td>Lumry et al</td>
<td>17</td>
<td>76†</td>
<td>325-2,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baldocchi et al</td>
<td>9</td>
<td>0</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin and Culver</td>
<td>1</td>
<td>0</td>
<td>600-2,930</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiu</td>
<td>12</td>
<td>50</td>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bianco et al</td>
<td>6</td>
<td>0</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>5</td>
<td>20</td>
<td>60</td>
<td>20</td>
<td>600-2,400</td>
</tr>
</tbody>
</table>

*Only controlled study.
†Nonasthmatic rhinosinusitis patients; ASA intolerance by naso-ocular symptoms alone.
from this strictly anecdotal and not quantified report are confounded by the probable multiplicity of mechanisms of actions of ketotifen (eg, H1 antihistamine effect), it suggests the possibility of a way of desensitizing without first provoking a reaction. In our patients, sensitivity to mediator and to cholinergic stimuli appeared to remain intact since the response thresholds for bronchial histamine and methacholine challenges were unchanged after ASA desensitization. Perhaps research employing ASA desensitization may not only shed light on this common clinical enigma, but possibly this information also may provide clues as to why these patients often have a severe, refractory and idiopathic type

NOTE: The more complete bibliography used in preparing this review may be obtained from the authors.

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