

Aspirin and concomitant idiosyncrasies in adult asthmatic patients

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The nasal and respiratory symptoms observed after oral challenge to aspirin (ASA), tartrazine, and other nonsteroidal anti-inflammatory substances are best described as idiosyncratic reactions. A positive response to oral challenge, defined as a 20% fall in forced expiratory volume in 1 sec (FEV₁) from baseline for up to 4 hr, occurred in 44 of 230 patients with ASA, 11 of 277 with tartrazine, 2 of 93 with sodium salicylate, and 2 of 69 with acetaminophen. No one had a positive response to tartrazine, sodium salicylate, or acetaminophen who was not also positive to ASA. The dose of ASA causing a positive response was less than 5 grains in 95% of the patients. Of 50 patients with a suspicious history studied in detail, 96% of those with ASA idiosyncrasy had sinusitis and 71% had nasal polyps. Methacholine challenges and random circulating and sputum eosinophils did not differentiate patients with a negative challenge from those with a positive challenge. However, patients with a positive history and positive challenge had significantly more random nasal eosinophils than those with negative aspirin challenges. The term "aspirin triad" has outlived its usefulness since ASA idiosyncrasy can exist in patients lacking certain components of the triad. ASA idiosyncrasy is unsuspected in many patients and possibly overdiagnosed in others.

The frequency of adverse reactions to aspirin (ASA) reported in the literature varies considerably, depending on the criteria used to determine its presence, the patient population surveyed, and the inclusion or exclusion of angioedema and urticaria.¹

The term "idiosyncratic reaction" rather than allergic reaction or intolerance best describes the nasal and respiratory symptoms observed after oral challenges to ASA and other nonsteroidal anti-inflammatory substances which inhibit prostaglandin synthetase.² Urticaria and angioedema at times have been included as part of the syndrome, but the mechanism responsible for these manifestations may well be different than that which provokes nasal and respiratory symptoms.³ Although idiosyncratic reactions to ASA and other anti-inflammatory agents have important clinical implications, perhaps more important are idiosyncratic reactions to tartrazine (FD&C No. 5),

which is widely prevalent in our diets. Even though most patients with ASA idiosyncrasy can take sodium salicylate with impunity,⁴ Vane⁵ has shown that it also inhibits prostaglandin synthetase in high concentrations.

For the past 5 yrs at National Jewish Hospital we have attempted to more accurately diagnose ASA and related idiosyncrasies in our asthmatic patient population. With the use of incremental doses of these substances we have challenged a large number of patients in order to confirm the safety of our methods and determine the relationship of ASA and related idiosyncrasies to other clinical problems such as sinusitis and nasal polyposis.

MATERIALS AND METHODS

Patient selections

Patients were teenagers and adults ranging in age from 14 to 72 yr. They had reversible obstructive airways disease (asthma) and a positive bronchial inhalation challenge response to histamine and/or methacholine.^{6,7} A few met the American Thoracic Society's definition for chronic bronchitis,⁸ and many were on oral corticosteroids.

From late 1972 until the present, 304 patients, 42 (13.8% of them teenagers, were studied with 230 patients receiving oral challenges to ASA. Seventy-four patients were not challenged to ASA because of unequivocal histories of pos-

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TABLE I. Bronchial challenge of asthmatic patients to oral aspirin categorized by class*

Group	Total No. (%)	No. positive	% positive	% positive by class
Class I	29 (12.6)	4	13.8	9.1
Class II	142 (61.7)	11	7.7	25.0
Class III	18 (7.8)	2	11.1	4.5
Class IV	41 (17.8)	27	65.8	61.4
Total	230	44		

*A positive response was a fall in FEV₁ of 20% or greater.

Class I: No history of ASA idiosyncrasy, ASA ingested within 1 mo of admission; Class II: No history of ASA idiosyncrasy, ASA not ingested within 1 mo of admission; Class III: Uncertain history of ASA idiosyncrasy; Class IV: History of asthma attack within 24 hr following ASA ingestion.

TABLE II. Symptom frequency

		Rhinorrhea	Stuffiness	Urticaria
Aspirin	(n = 43)*	14 (p < 0.0005)	10 (p < 0.005)†	1 (NS)
Placebo	(n = 43)	0	1	0
Tartrazine	(n = 6)‡	3 (p < 0.05)	0	0
Placebo	(n = 6)	0	0	0

*One patient excluded because of lack of placebo control.

†Four of these patients also had rhinorrhea (included in the 14).

‡Five patients excluded because of lack of placebo control.

itive, severe reactions. Tartrazine challenges were performed on 277 patients, sodium salicylate challenges on 93 patients, and acetaminophen challenges on 69. A single patient might have received one, two, or three of the above challenges. All signed an informed consent.

Materials

The following drugs were used: aspirin (J. T. Baker Co., Phillipsburg, N. J.), acetaminophen (McNeil Laboratories, Fort Washington, Pa.), sodium salicylate (J. T. Baker Co., Phillipsburg, N. J.), tartrazine, practical grade (J. T. Baker Co., Phillipsburg, N. J.), and lactose (J. T. Baker Co., Phillipsburg, N. J.). Each challenge capsule was prepared by the National Jewish Hospital Pharmacy according to standard pharmacy procedure using lactose as the excipient and standard gelatin capsules so that the total weight of the test materials plus lactose equaled 200 mg.

Challenge procedures

Prior to testing, a detailed history was elicited and the patients were divided by history into the following four categories:

Class I: Patients with no history of ASA idiosyncrasy who had ingested ASA within 1 mo of admission.

Class II: Patients with no history of ASA idiosyncrasy who had ingested no ASA for at least 1 mo before admission.

Class III: Patients who by history were uncertain of the relation of their asthma attacks to ASA ingestion.

Class IV: Patients who by history had asthma attacks within 24 hr following ingestion of ASA.

For the purposes of the oral challenges, classes I and II were treated similarly and classes III and IV were treated similarly. All bronchodilators and antihistamines were withheld for 6 to 12 hr prior to testing. Corticosteroids were not withheld. Occasionally, patients with an unstable baseline forced expiratory volume in 1 sec (FEV₁) had their medications held for less than 6 hr.

Classes I and II were screened by a double-blind trial with sequential administration of 75, 325, and 650 mg of ASA randomized with placebo on different days. Classes III and IV were screened by a double-blind sequential trial of 15, 37.5, 75, 150, 325, and 650 mg of ASA randomized with placebo on different days. A fall in FEV₁ of 20% or greater compared with baseline for up to 4 hr after ASA administration was considered a positive test. Any questionable response resulted in a repetition of the suspected dose double-blinded with placebo.

Initially, tartrazine challenges were performed with increasing doses in a manner similar to the ASA challenges. Presently the challenge dose is guided by a detailed history with specific questions regarding tolerance or intolerance to certain foods known to contain tartrazine. Patients with negative ASA challenge and negative ASA and tartrazine history receive 50 mg of tartrazine. Patients with a positive ASA challenge who give a positive or questionable history of tartrazine sensitivity receive in a double-blind manner 1, 5, 15, 25, and 50 mg of tartrazine randomized with placebo on separate days. Questionable results are repeated with placebo in a double-blind fashion.

The doses of sodium salicylate and acetaminophen used for challenge were 600 and 650 mg, respectively. In pa-

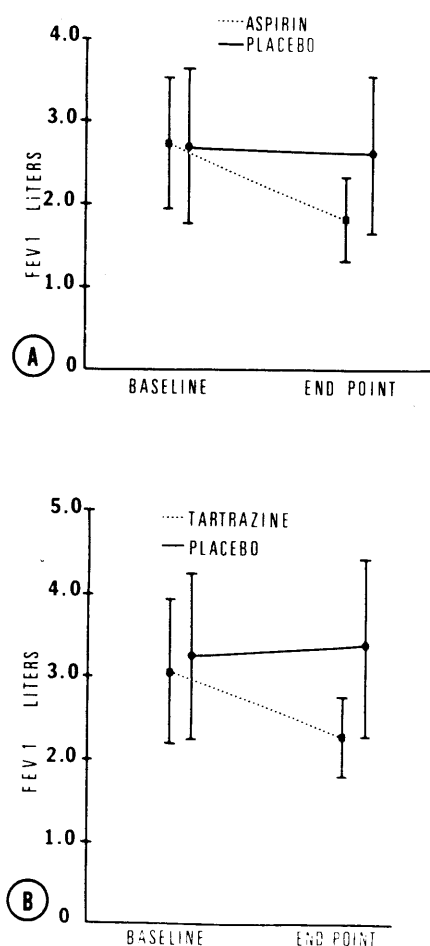


FIG. 1. A, Comparison of the fall in FEV₁ ($\pm$ SEM) after oral challenge with ASA and placebo. B, The fall after tartrazine and placebo.

TABLE III. Number of patients with a positive response* to ASA and tartrazine categorized by class and dose

	Dose (mg)	Class†			
		I	II	III	IV
Aspirin	10				1
	15				1
	37.5				7
	75	1	9	1	11
	90				2
	150	1	2		3
	325	2			1
	650			1	1
Tartrazine	1	1			2
	5		1		4
	15				1
	25				2

*A positive response was a fall in FEV₁ of 20% or greater.

†See Table I and text for explanation of classes.

tients with a positive ASA challenge and a suspicious history, the medication was tested incrementally as with ASA, beginning with that dose which provoked a positive ASA challenge.

Challenges were monitored with half-hourly pulmonary function studies including forced vital capacity (FVC), FEV₁, and peak expiratory flow during the middle half of the FVC (FEF 25% to 75%). Patients were observed for rhinorrhea, which often precedes a drop in pulmonary function. A positive test was considered to be a fall in FEV₁ of 20% or greater within 4 hr. Pulmonary function measurements were performed on the Medistor pulmonary function analyzer (Simlog Instruments, Inc., Redmond, Wash.) calibrated with a 1.5 L syringe. The rated accuracy reproducibility of the Medistor spirometer, confirmed in our laboratory, is within $\pm 5\%$. The best of two consistent forced expiratory efforts were recorded on each occasion. Patients were tested only when their FEV₁ was equal to or exceeded 80% of their best known function.

In a separate analysis, details in the history of 50 patients were tabulated to determine the frequency of other characteristics that might be present. None of the 50 patients had a known severe reaction to ASA. These patients were selected from a separate study involving platelets. The other data mentioned in Table IV were also recorded from them.

RESULTS

The responses of the 230 asthmatic patients challenged, categorized according to class, are shown in Table I. Interestingly, about 35% of the patients with a strong history of an adverse reaction to ASA nevertheless had a negative oral challenge. Also, 15 patients in classes I and II, i.e., 8.8% of those patients with no history or suspicion of ASA idiosyncrasy, had a positive ASA challenge. Of the 44 with positive challenges, 4 (9%) were teenagers.

Fig. 1, A compares the fall in FEV₁ $\pm$ SEM after challenge with ASA and placebo. The mean fall in FEV₁ for 42 of the 44 patients (two patients were too ill to perform pulmonary functions) was 34.07%. Eighteen patients fell between 20% and 30%, 12 patients between 30% and 40%, 10 patients between 40% and 50%, one patient between 50% and 60%, and one patient between 60% and 70%. There was a significant decrease in FEV₁ from baseline for ASA (2.71 $\rightarrow$ 1.82) compared with placebo (2.69 $\rightarrow$ 2.64) ($p < 0.0005$). There was no statistical difference between the baseline FEV₁ for the two agents. The mean end test time for aspirin was 2.3 hr and for placebo > 4.0 hr ($p < 0.0005$). Table II lists the symptoms observed after challenge. Table III categorizes the patients according to class and dose and shows that even those subjects who denied positive histories could develop a positive reaction at relatively low challenge doses.

Laboratory tests of the previously mentioned 50

TABLE IV. Demographic and laboratory findings of 50 asthmatic patients with uncertain or suspicious histories for ASA idiosyncrasy

	Positive challenge	Negative challenge	Significance
No. in group (mean $\pm$ SE)	27	23	
Age (yrs) (mean $\pm$ SE)	34.3 $\pm$ 2.7	40.8 $\pm$ 2.8	p < 0.05
Sex (mean % males $\pm$ SE)	37.0 n = 27	30.4 n = 23	NS
% positive tartrazine challenge	33.3 n = 21	0 n = 22	p < 0.01
% with nasal polyps	70.8 n = 24	34.8 n = 23	p < 0.05
% with sinusitis	96.2 n = 26	60.9 n = 23	p < 0.01
% with positive skin test	46.2 n = 26	39.1 n = 23	NS
Histamine challenge mean threshold dose (mg/cc)	2.45 $\pm$ 0.59 n = 21	2.89 $\pm$ 0.74 n = 21	NS
% positive bronchial challenge to other antigens	23.8 n = 21	11.1 n = 18	NS
Circulating eosinophils	564.7 $\pm$ 140.5 n = 25	381.7 $\pm$ 91.2 n = 20	NS
Nasal eosinophils	22.5 $\pm$ 6.0 n = 25	8.6 $\pm$ 4.1 n = 23	p < 0.01
Sputum eosinophils	26.7 $\pm$ 8.1 n = 20	23.0 $\pm$ 7.8 n = 20	NS

patients with uncertain or suspicious histories of ASA idiosyncrasy were analyzed in detail, and the results are shown in Table IV. There were four teenagers with positive challenges and three teenagers with negative challenges. There were no sex differences in any of the groups. Interestingly, no individual with a negative ASA challenge had a positive tartrazine challenge. Approximately one of three individuals with a positive ASA challenge in this select group had a positive tartrazine challenge, and 71% had nasal polyps. About 35% of the asthmatics with a negative ASA challenge had nasal polyps. Although the incidence of sinusitis by roentgenogram is approximately 60% in the total asthmatic population (confirmed in a separate study), 96% of the ASA-idiosyncratic patients had sinusitis by roentgenogram. Skin test reactivity or bronchial challenge reactivity to aeroallergens did not help differentiate the ASA-idiosyncratic patients from the others. Excluding those patients whose medications could not be withheld and those receiving troleandomycin, methacholine challenges did not differentiate the groups.^{6, 7} Also, the degree of responsiveness to a bronchial inhalation challenge with histamine had no predictive value.^{6, 7} Eosinophils present in the circulation, nasal smear, or sputum, determined at random times, did not show a difference, with the exception that patients with a negative history and negative challenge had significantly fewer nasal eosinophils than those with a positive ASA challenge.

The response of the asthmatic patients challenged to tartrazine, sodium salicylate, and acetaminophen compared to ASA is shown in Table V. Fig. 1, B shows the fall in FEV₁ $\pm$ SEM after challenge with tartrazine and placebo. There was a significant decrease in FEV₁ from baseline after tartrazine (3.08 $\rightarrow$ 2.28) compared with placebo (3.25 $\rightarrow$ 3.38) (p <

TABLE V. Response of asthmatic patients challenged to oral tartrazine, sodium salicylate, acetaminophen, and ASA

	No. tested	No. positive	% positive
Tartrazine	277	11	4.0
Sodium salicylate	92	2	2.2
Acetaminophen	69	2	2.9
ASA	230	44	19.1

0.0005). There was no statistical difference between FEV₁ at baseline for tartrazine vs placebo. The mean end test time for tartrazine was 2.3 hr and for placebo > 4.0 hr (p < 0.0005). Fifty percent of the patients who were positive experienced rhinorrhea (Table II). All of these patients also experienced rhinorrhea with their ASA challenge. Only a few patients had a significant fall in FEV₁ following sodium salicylate and acetaminophen challenges. Fig. 2, A shows the FEV₁ of the two patients with positive challenges to sodium salicylate and Fig. 2, B, the two patients with positive challenges to acetaminophen. Unfortunately, this disallows their categorization as totally innocuous substitutes for ASA. The doses at which patients fell to sodium salicylate were 37.5 and 600 mg, and those doses for acetaminophen were 30 and 325 mg. Not a single patient had a positive response to tartrazine, sodium salicylate, or acetaminophen who was not also positive to ASA.

DISCUSSION

The incidence of ASA idiosyncrasy depends on the criteria used to determine its presence, such as the inclusion or exclusion of angioedema or urticaria and the population surveyed. In general, statistics based on historical data assume a lower incidence than those

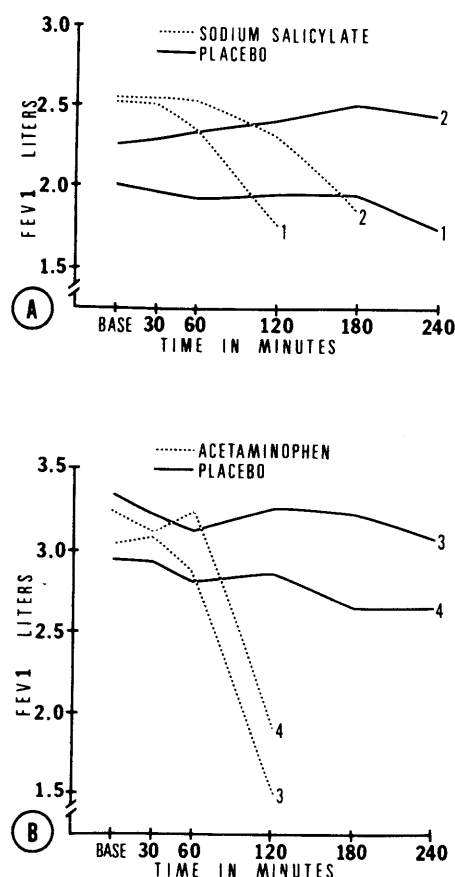


FIG. 2. A, Comparison of fall in FEV₁ of two patients after oral challenge to sodium salicylate and placebo. B, Two other patients after acetaminophen and placebo.

based on oral challenges. Falliers⁹ found an incidence of 1.9% in the 1,298 children's charts he studied. Although Settupane et al.¹⁰ found twice that incidence in the asthma group of 731 older patients they studied, the incidence in both these studies is much less than that reported by those employing oral challenge. Vedanthan et al.,¹¹ utilizing our method of oral provocation, found a 13% incidence of ASA idiosyncrasy in a pediatric population. They felt that "the much lower incidence of adverse ASA responses reported by Falliers at the same center probably reflects the errors inherent in such long-term retrospective studies where heavy reliance must be placed upon the completeness of written records." Another pediatric study by Rachelefsky et al.¹² revealed a higher incidence (28%) of ASA idiosyncrasy employing oral challenges.

In adult studies Giraldo et al.¹³ found a 5.6% incidence in 68 university patients with asthma and a 3% incidence in 75 Veterans Administration Hospital patients with asthma, using historical criteria. Yet, Van Leeuwen¹⁴ and McDonald et al.¹⁵ found a 16% and

8% incidence, respectively, using oral challenge. We found a 19% incidence in our adult population using oral challenge and a 39% incidence when challenge and historical data were combined. The fact that 15 out of 171, or 8.8%, had no history or suspicion of ASA idiosyncrasy despite a positive ASA challenge implies that this entity is not suspected in many individuals. On the other hand, since about 35% of the people who were quite certain they had ASA idiosyncrasy had a negative challenge, it may be overdiagnosed in others. Other explanations such as temporary refractory periods or changing or increased thresholds, are also possible. In fact, we had one carefully documented situation of a patient with a known positive oral challenge who also had an abnormal collagen-induced platelet aggregation. The platelet aggregation study reverted to normal prompting rechallenge with ASA, to which the patient became negative at 600 mg. Greater doses of drugs such as ASA and tartrazine might have revealed more positive responders; however, there would be more side effects and risk to the patient with such challenges.

Regarding tartrazine intolerance, Samter and Beers¹⁶ found that 3 of 40 ASA-intolerant patients could not tolerate this FD&C No. 5 dye. Juhlin et al.¹⁷ reported that none of their 54 asthmatic children had tartrazine-induced bronchospasm. Stenius and Lemole¹⁸ studied 26 patients with both agents. A positive response was a fall in peak expiratory flow of 20% or more. The maximum dose of ASA they employed was 100 mg and of tartrazine 10 mg, which the authors admit may be relatively low. About 25% of the patients had a positive ASA provocation test, which underdiagnosed the real incidence, since patients with a definite history of ASA sensitivity were not tested. Slightly more than 20% of the tartrazine challenges were positive. However, of the 26 patients challenged with both ASA and tartrazine, about 50% of the positive ASA patients also had a positive tartrazine test. This high figure is in keeping with studies of others.¹⁹ Interestingly, 65% had no suspicion that they would have an adverse reaction to ASA. In our adult population, up to one third of the patients with suspected ASA idiosyncrasy also developed asthma after ingesting tartrazine (see Table V). Samter and Beers¹⁶ felt that sodium salicylate was a substance that asthmatic ASA-idiosyncratic patients could take with impunity, an observation not entirely in keeping with our experience. Although Smith,²⁰ in an unblinded study, reported that three of five patients with ASA-induced asthma had a greater than 30% fall in FEV₁ after 500 mg of acetaminophen, only two of our patients had a positive bronchial challenge to acetaminophen. These statistics imply that adequate label-

ing and knowledge of ASA and tartrazine-containing compounds is important and that references should be sought for updated lists of substances containing ASA and tartrazine.¹ It is apparent that the concept of the ASA triad of asthma, sinusitis, and nasal polyps in a patient with ASA idiosyncrasy may be misleading. Sinusitis is definitely a clue to its existence and was found in 96% of our patients with suspected ASA idiosyncrasy. Nasal polyps were found in 71% of our selected population. However, these might be late signs, since we have observed some patients with intractable rhinorrhea who improve after discontinuation of ASA. Family studies support "forme fruste" of the triad.²¹ Falliers⁹ reported on two distinct pediatric groups: a reagin-mediated positive family history with a near-zero risk for ASA idiosyncrasy and a late-onset, nasal polyps, and no eczema group in which ASA idiosyncrasy was found. However, this differentiation is impractical and somewhat arbitrary. Positive skin tests can also be found in ASA-idiosyncratic groups, since reagin may be present but not responsible for symptoms. Yunginger et al.²² found four patients in the group considered by Falliers to be low risk. These four had no history of nasal polyps but did have seasonal history, family history of allergies, and positive skin tests. Rachelefsky¹² in his pediatric study could not differentiate ASA-idiosyncratic patients from others by their steroid dependency, frequency of eczema, nasal eosinophilia, serum IgE levels, and peripheral eosinophil count. In our experience, contrary to that of Samter,²³ laboratory data such as increased blood eosinophil count and increased reactivity to methacholine and histamine did not differentiate ASA-reactive asthmatics from others. However, nasal eosinophil counts may prove useful. Our technique for challenging patients was safe. We were not comfortable with an endpoint of a 50% fall in FEV₁ such as was employed by McDonald et al.¹⁵

All but two of the 44 patients positive to ASA (95%, Table III) were unable to tolerate a single five-grain tablet of ASA. Delaney²⁴ also used increasing doses of ASA for challenges in a single-blind study. Of the 41 of 42 who responded, a few patients were positive to each of the doses administered. Thus 5 patients were positive at 30 mg, 2 patients at 60 mg, 16 patients at 100 mg, 4 patients at 300 mg, and 8 patients at 600 mg. Paracetamol (acetaminophen) 500 mg resulted in increased airways obstruction in 12 (28.6%) of these same patients. Patients with a history of the condition were highly sensitive and reactive to small doses of ASA or to paracetamol. Patients who were previously unaware of ASA idiosyncrasy were less sensitive. They required larger challenge

doses of ASA and did not respond to paracetamol challenge. From these observations he inferred that paracetamol was a relatively weak inhibitor of prostaglandin synthesis.

The most recent and perhaps most popular theory to explain the adverse reaction of patients with ASA idiosyncrasy involves inhibition of biosynthesis of prostaglandin. Although the E family of prostaglandins produces bronchodilatation and the F series bronchoconstriction, it is not clear if or how a change in the usual E-F ratio elicits symptoms in a given patient.

The following observations do not support the prostaglandin theory. Although indomethacin, mefenamic acids, flufenamic acid, and phenylbutazone produce the syndrome and inhibit prostaglandin synthetase as well, Gerber et al.²⁵ reported that tartrazine does not inhibit the synthetase, yet it causes symptoms in a subgroup of ASA idiosyncratic patients. An interesting observation noted by others and by us is that certain patients can actually improve their pulmonary functions after ingestion of ASA.^{26, 27} Basomba et al.²⁸ found that cromolyn sodium blocked oral provocation tests with ASA to varying degrees in two thirds of the 17 patients studied. This observation suggests that mast cell degranulation has been blocked by cromolyn and does not support the prostaglandin hypothesis.

In conclusion, ASA idiosyncrasy probably is still an underdiagnosed problem in asthmatic patients. We do not advocate routine ASA challenges, not because of bronchoconstriction, which is easily reversed, but because of the uncomfortable rhinorrhea and sinus symptoms that can persist for weeks in some patients. Thus from a practical standpoint we tell asthmatic patients to avoid ASA or other anti-inflammatory medications such as described by Szczeklik et al.²⁹

On the other hand, oral challenges may be the only way to confirm ASA or related idiosyncrasy in asthmatic patients who may require a potent anti-inflammatory agent due to a concomitant disease such as rheumatoid arthritis. The oral challenge procedure described can be done relatively safely. The presence of ASA idiosyncrasy is often a clue to an adverse reaction to tartrazine, acetaminophen, and sodium salicylate.³⁰

Patients with known ASA idiosyncrasy whose asthma has been refractory to treatment may well have as yet undiagnosed tartrazine idiosyncrasy and should be given an oral challenge to tartrazine. Substances such as FD&C No. 5 are much more difficult to avoid in the patient's diet, and thereby have far-reaching implications.

Acetaminophen and sodium salicylate in the usual

doses are possible alternatives; however, an occasional patient may develop an idiosyncratic or adverse reaction to these substances. Accordingly, if an ASA-idiosyncratic individual using either acetaminophen or sodium salicylate continues to do poorly, we recommend an oral challenge in this case as well.

REFERENCES

1. Harnett JC, Spector SL, Farr RS: Aspirin idiosyncrasy, asthma, and urticaria, in Middleton E, Reed C, Ellis E, editors: *Allergy: Principles and practice*. St. Louis, 1978, The C. V. Mosby Co.
2. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G: Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attack in aspirin-sensitive patients. *Br Med J* **1**:67, 1975.
3. Settipane GA, Pudupakkam RK: Aspirin intolerance. III. Subtypes, familial occurrence and crossreactivity with tartrazine. *J ALLERGY CLIN IMMUNOL* **56**:215, 1975.
4. Samter M, Beers RF: Concerning the nature of intolerance to aspirin. *J ALLERGY* **40**:281, 1967.
5. Vane JR: The mode of action of aspirin and similar compounds. *J ALLERGY CLIN IMMUNOL* **58**:691, 1976.
6. Spector SL, Farr RS: A comparison of methacholine and histamine inhalations in asthmatics. *J ALLERGY CLIN IMMUNOL* **56**:308, 1975.
7. Spector SL, Farr RS: Bronchial inhalation procedures in asthmatics. *Med Clin North Am* **58**:71, 1974.
8. American Thoracic Society: Chronic bronchitis, asthma, and pulmonary emphysema: A statement by the Committee on Diagnostic Standards for Nontuberculosis Respiratory Disease. *Am Rev Respir Dis* **85**:762, 1962.
9. Falliers CJ: Aspirin and subtypes of asthma: Risk factor analysis. *J ALLERGY CLIN IMMUNOL* **52**:141, 1973.
10. Settipane GA, Chaffee FH, Klein DE: Aspirin intolerance. II. A prospective study in an atopic and normal population. *J ALLERGY CLIN IMMUNOL* **53**:200, 1974.
11. Vedanthan PR, Menon MM, Bell TD, Bergin D: Aspirin and tartrazine oral challenge: Incidence of adverse response in chronic childhood asthma. *J ALLERGY CLIN IMMUNOL* **60**:8, 1977.
12. Rachelefsky GS, Coulson A, Siegel SC, Stiehm ER: Aspirin intolerance in chronic childhood asthma: Detected by oral challenge. *Pediatrics* **56**:443, 1975.
13. Giraldo B, Blumenthal MN, Spink WW: Aspirin intolerance and asthma. A clinical and immunological study. *Ann Intern Med* **71**:479, 1969.
14. Van Leeuwen WS: Pathognomonische bedeutung der eubermfindlichkeit gegen aspirin bei asthmatikern. *Much Med Wochenschr* **75**:1588, 1928.
15. McDonald JR, Mathison DA, Stevenson DD: Aspirin intolerance in asthma, detection by oral challenge. *J ALLERGY CLIN IMMUNOL* **50**:198, 1972.
16. Samter M, Beers RF: Intolerance to aspirin. Clinical studies and consideration to its pathogenesis. *Ann Intern Med* **68**:975, 1968.
17. Juhlin L, Michaëlsson G, Zetterström O: Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *J ALLERGY CLIN IMMUNOL* **50**:92, 1972.
18. Stenius BS, Lemola M: Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clin Allergy* **6**:119, 1976.
19. Bernstein IL, Johnson CL, Gallagher JS, Archer D, Johnson H: Are tartrazine reactions mediated by IgE? *J ALLERGY CLIN IMMUNOL* **61**:208, 1978. (Abst.)
20. Smith AP: Response of aspirin-allergic patients to challenge by some analgesics in common uses. *Br Med J* **2**:494, 1971.
21. Von Maur K, Adkinson NJ Jr, Van Metre TE Jr, Marsh DG, Norman P: Aspirin intolerance in a family. *J ALLERGY CLIN IMMUNOL* **54**:380, 1974.
22. Yunginger JW, O'Connell EJ, Logan GB: Aspirin-induced asthma in children. *J Pediatr* **82**:218, 1973.
23. Samter M: Intolerance to aspirin. *Hosp Pract* **8**:85, 1973.
24. Delaney JC: The diagnosis of aspirin idiosyncrasy by analgesic challenge. *Clin Allergy* **6**:177, 1976.
25. Gerber JG, Payne A, Oelz O, Nies AS, Oates JA: Tartrazine and the prostaglandin system. *J ALLERGY CLIN IMMUNOL* **63**:289, 1979.
26. Kordansky D, Adkinson NF, Norman PS, Rosenthal RR: Asthma improved by non-steroidal anti-inflammatory drugs. *Ann Intern Med* **88**:508, 1978.
27. Farr RS, Spector SL, Wangaard C: Asthma and non-steroidal anti-inflammatory drugs. *Ann Int Med* **89**:577-578, 1978.
28. Basomba A, Romar A, Pelaez A, Villalmanzo IG, Campos A: The effect of sodium cromoglycate in preventing aspirin-induced bronchospasm. *Clin Allergy* **6**:269, 1976.
29. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G: Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J ALLERGY CLIN IMMUNOL* **60**:276, 1978.
30. Farr RS: Asthma in adults: The ambulatory patient. *Hosp Pract* **13**:113, 1978.