

Aspirin intolerance in asthma

Detection by oral challenge

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Oral aspirin challenge was used to detect aspirin intolerance in selected asthmatic patients who did NOT give a history of asthma following aspirin ingestion. Forty-two asthmatic patients with either nasal polyps, sinusitis, or severe asthma requiring corticosteroid therapy were challenged with aspirin. Under carefully controlled circumstances and at a time when their asthma was stable, patients ingested 640 mg. of aspirin (Ascriptin) after taking all their usual maintenance medications. Several parameters of lung function and clinical symptomatology were followed serially over a 4 hour period. Eight of 42 challenges were positive. When these patients were combined with 14 patients who were intolerant to aspirin by history, the prevalence of aspirin intolerance in our asthmatic population was 8 per cent. Patients who were intolerant to aspirin showed a statistically significant increase in the prevalence of the hallmark criteria of nasal polyps, sinusitis, and steroid dependency when compared to all new asthmatic patients during a 2 year period. Aspirin challenge in selected patients can detect aspirin intolerance not recognized by history alone. These patients can be warned to avoid aspirin ingestion in the future. In addition, their management can be improved by recognizing this variant of the asthma syndrome.

For over fifty years, adverse effects from aspirin ingestion have been noted.¹ Many reactions, including urticaria, angioedema, purpura, rhinitis, thrombocytopenia, and pancytopenia, have been reported.¹⁻⁵ The sudden onset of asthma after aspirin ingestion is a type of reaction which is of considerable interest and concern to allergists. Asthmatic episodes may occur from minutes to hours after ingestion of aspirin-containing substances^{1, 3} and range from mild, brief, easily treated attacks to severe protracted asthma with cyanosis, coma, and, rarely, death.⁶⁻⁹ Aspirin-intolerant patients frequently have accompanying sinusitis and nasal polyps.^{10, 11}

Aspirin intolerance has been most frequently recognized in patients who give a history of severe asthma precipitated by ingestion of aspirin. Some aspirin-intolerant patients, however, are not aware that aspirin will provoke an asthma attack.^{12, 13} If these patients could be identified, they could be protected from future aspirin ingestion. However, attempts to identify these patients

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by skin testing^{1, 10, 14} and other techniques which do not involve direct oral challenge have been unsuccessful.^{10, 15} Oral challenge with aspirin has been reported^{12, 16, 18} In 1928, Van Leeuwen¹⁶ reported giving aspirin to 100 consecutive asthmatic patients with no previous history of aspirin intolerance. He noted significant symptoms of asthma in 16 per cent. Other authors,^{17, 18} using different techniques and patient selection methods, have reported varying results after oral challenge. In this study, we have challenged certain asthma patients with aspirin in order to identify a previously unknown subpopulation of asthmatic patients. The direct advantages of this diagnostic approach are: more accurate subclassification of our asthma population, improved management of individual patients, and avoidance of future aspirin-induced catastrophes.

MATERIALS AND METHODS

Patients with an unequivocal history of asthma after taking aspirin were considered aspirin intolerant and were not challenged. Forty-two asthmatic patients with a negative or uncertain history for an asthma attack following aspirin ingestion were selected for aspirin challenge on the basis of having one or more of the following characteristics: nasal polyps, sinusitis, or severe asthma requiring maintenance glucocorticoid therapy. One hundred other asthmatic patients who possessed these characteristics were not available for aspirin challenge.

On the morning of challenge, the absence of respiratory tract symptoms was confirmed by a physical examination and by spirometry with the use of a Jones Pulmonor.* The patient ingested his usual maintenance medications including corticosteroids. He then ingested two Ascriptin tablets (each containing 320 mg. of aspirin and 150 mg. of magnesium aluminum hydroxide) and was informed the tablets may or may not contain aspirin. Ascriptin was used because it was similar in size and appearance to Maalox (400 mg. of magnesium aluminum hydroxide per tablet) which was used for the control challenge and because Ascriptin did not closely resemble most aspirin tablets. Serial observations of subjective symptoms, chest examination, forced expiratory volumes, and flow rates were recorded at ½, 1, 2, 3, and 4 hours and more frequently if symptoms appeared. Serial serum salicylate levels were obtained during selected challenges. A rapid reduction of 50 per cent or more in the one-second forced expiratory volume (FEV₁) was arbitrarily chosen to indicate a positive asthmatic response. Because patients received their usual maintenance medications, FEV₁ values remained stable until the onset of the sudden asthmatic response. At another time, a control challenge with Maalox tablets, tartrazine, or acetaminophen did not produce a drop of the FEV₁ in the patients with a positive aspirin challenge.

Charts of 282 new Scripps Clinic and Research Foundation patients with a diagnosis of asthma during the 2 years beginning July, 1969, were reviewed. Age, sex, history of aspirin intolerance, presence or absence of nasal polyps, sinusitis, or rhinitis, requirement for corticosteroid therapy, and presence or absence of skin-sensitizing antibodies (SSA) were noted. SSA were determined by intradermal skin tests with common inhalant and ingestant allergens.† Sinusitis was considered to be present if x-rays revealed either mucoperiosteal thickening, air-fluid levels, or opacification of one or more paranasal sinuses. The presence of nasal polyps was confirmed by an otorhinolaryngologist in all but 2 patients.

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†Specific skin-sensitizing antibody was presumed to be present if an intradermal injection of 0.02 ml. of an aqueous extract (Hollister-Stier) within 15 minutes evoked a dermal wheal greater than 7 mm. by 7 mm. (perpendicular diameter) and similar injection of 0.45 per cent phenol in saline produced a wheal less than 3 mm. by 3 mm. The following test substances were used: individual animal dander or feathers (9 species), vegetable fibers (3 varieties), house dust to a maximum concentration of 1:100 w/v; mixtures of tree pollen (10 species), grass pollen (8 species), weed pollen (10 species), and Bermuda or Johnson grass pollen to a maximum concentration of 1:1,000 w/v; mold spores (5 species) at a concentration of 1:200 w/v; and food (chocolate, egg, milk, peanut, or wheat) to a maximum concentration 1:500.

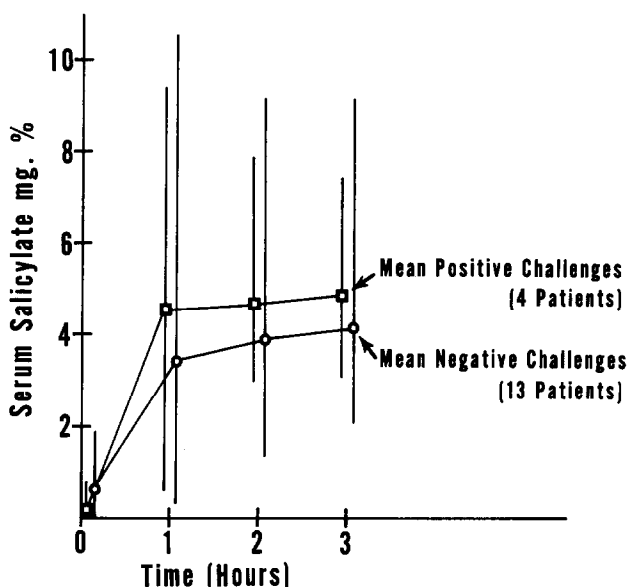


FIG. 1. Serum salicylate levels during aspirin challenges. Open squares are means of 4 aspirin-positive patients. Open circles are means of 15 aspirin-negative patients. Bars represent total range of recorded values.

RESULTS

Eight of the 42 aspirin challenges were positive. In these patients, the onset of severe respiratory symptoms was precipitous, as though the entire respiratory tree was suddenly activated. Seven of the 8 patients developed conjunctival injection, profuse rhinorrhea, and cutaneous flushing. This precipitous reaction began between 45 and 150 minutes (mean, 84 minutes) after the ingestion of aspirin. Induced asthmatic episodes were reversed in all cases with the administration of subcutaneous epinephrine, intravenous aminophylline, and corticosteroids, and inhaled isoproterenol delivered by an intermittent positive-pressure breathing (IPPB) apparatus. In 2 of 6 outpatients, recovery was gradual and overnight inpatient observation was carried out. Six patients felt exhausted for 24 hours following a positive aspirin challenge. Patients with a negative challenge did not experience symptoms or require treatment. Serial salicylate levels, obtained during aspirin challenges, increased from base-line values in a variable manner which bore no relationship to the onset of the asthma episode and did not differ from those patients who experienced a negative aspirin challenge (Fig. 1).

Of the 282 new asthmatic patients seen at our institution during the 2 year period, 260 were examined by members of the Allergy and Immunology Division. There was a recorded statement in the chart as to presence or absence of aspirin intolerance for 175 patients. Of these, 151 had no history of adverse effects from aspirin, 10 gave an uncertain history, and 14 gave a definite history of asthma following aspirin ingestion.

The 14 patients who gave a history of aspirin intolerance were combined

TABLE I. Comparison of patients intolerant to aspirin with total asthmatic population

Patient data	Total new asthma patients, 1969-1971	Patients intolerant to aspirin, 1969-1971
No. of Patients	282	22 (8%)
Mean age	38.7	48.6*
Females (%)	52	68
Sinusitis	106 (38%)	19† (86%)
Nasal polyps	38 (13%)	13† (59%)
On steroids	94 (33%)	20† (91%)
Positive skin tests	205 (73%)	15 (68%)

*p = < 0.01 (Student's t test).

†p = < 0.001 (chi square).

TABLE II. Comparisons within the population of asthmatic patients intolerant to aspirin

Patient data	Aspirin-intolerant asthmatic patients	
	Positive history	Positive challenge
No. of patients	14	8
Mean age	51.9	42.8
Females (%)	71	62
Sinusitis	11* (79%)	8* (100%)
Nasal polyps	8* (57%)	5* (62%)
On steroids	12* (86%)	8* (100%)
Positive skin tests	7† (50%)	8† (100%)

*p > 0.05 by chi square.

†p < 0.05 by chi square.

TABLE III. Number of hallmarks* present in groups of asthmatic patients

Hallmarks	Aspirin intolerant by history (14)	Aspirin intolerant by challenge (8)	Negative aspirin challenge (34)	Remaining asthmatic patients (226)
None	1	0	0	126
One	2	0	19	62
Two	4	3	9	34
Three	7	4	5	4
Four	0	1	1	0

*Sinusitis, polyps, corticosteroid dependence, and uncertain history of aspirin intolerance.

with the 8 who had a positive aspirin challenge. They were compared with the total group of 282 asthmatic patients (Table I). The aspirin-intolerant patients were older and had an increased incidence of sinusitis, nasal polyps, and treatment with corticosteroids. There was a similar frequency of positive intradermal skin tests in both groups.

The 14 patients with a positive history were compared with the 8 patients who had a positive challenge in Table II. The slight differences between these groups were not significant except for the increased incidence of positive skin tests in those patients with a positive challenge. It is important to note that the patients who gave a history of aspirin intolerance were not selected because they had sinusitis, nasal polyps, or required corticosteroid treatment. Yet, the incidence of the hallmark criteria in this group did not differ significantly from that in the patients with a positive aspirin challenge. Table III indicates that aspirin intolerance, either by history or by challenge, was unusual in patients

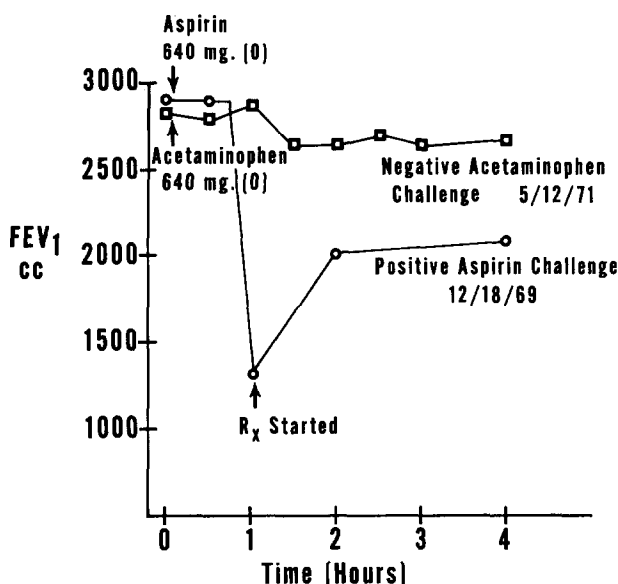


FIG. 2. Aspirin and acetaminophen challenges (Patient G. J.). Fifty minutes after aspirin (open circles) was ingested, patient developed conjunctival injection, rhinorrhea, cutaneous flushing, wheezing, and dyspnea. A control (open squares) challenge, using acetaminophen, resulted in no signs, symptoms, or FEV₁ changes.

who had fewer than two of the characteristic hallmarks. The majority of aspirin-intolerant patients had two (7/22) or more (12/22) of these characteristics. Fifteen of the 34 patients who underwent a negative aspirin challenge also had two or more hallmark criteria, indicating that the presence of these criteria alone was not sufficient evidence for identifying aspirin intolerance. Aspirin challenge was not undertaken in 38 patients who had two or three of the characteristics. One would expect additional patients with aspirin intolerance to be hidden in this group.

CASE REPORTS

The following case reports exemplify the overall results.

Case 1

G. J., a 34-year-old woman, was well until September, 1966, when she developed sneezing and profuse rhinorrhea during exposure to winds from inland deserts. In October, 1967, she reported paranasal headaches and green nasal discharge. In January, 1969, she experienced a flu-like illness and a month later noted nocturnal wheezing. Over the next 6 months her asthma persisted while she was following a nonsteroid treatment program of Tedral and antihistamines. On three occasions she experienced sudden, unexplained episodes of severe wheezing and dyspnea lasting 12 hours. On physical examination the nasal mucosa was red, and there were small polyps in the nasal attic. The maxillary sinuses did not transilluminate. On auscultation, the chest was filled with inspiratory and expiratory wheezes. Sinus x-rays showed bilateral maxillary mucoperiosteal thickening. Positive wheal and flare skin test reactions were detected. In December, 1969, an aspirin challenge was positive (Fig. 2). Fifty minutes after ingesting 2 Ascriptin tablets (640 mg. of aspirin), the patient developed

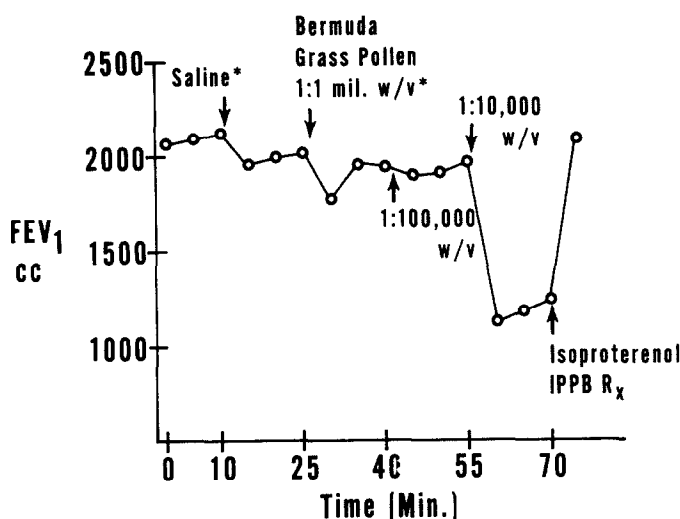


FIG. 3. Positive bronchial inhalation challenge (Patient G. J.). A positive challenge (20 per cent fall of FEV₁), using 1:10,000 w/v Bermuda grass extract, produced wheezing and dyspnea but no other symptoms or signs. *Saline, 1 c.c., and 1 c.c. of each dilution of the extract was inhaled using a DeVilbiss No. 40 nebulizer and a compressed air source.

rhinorrhea, facial flushing, conjunctival injection, chest tightness, and dyspnea. There was a sudden 60 per cent fall in the FEV₁ from the base-line values. Bronchospasm was slowly reversed by treatment with epinephrine, intravenous aminophylline, corticosteroids, and isoproterenol delivered by IPPB apparatus. Alternate-day prednisone (10 to 15 mg.) and other oral bronchodilators were initiated. An otorhinolaryngologist confirmed the presence of bilateral purulent sinusitis and performed bilateral antrostomies. In March, 1971, the patient confused aspirin tablets with vitamin C tablets and inadvertently ingested 2 aspirin tablets. Fifty minutes later she experienced intense rhinorrhea, lacrimation, and chest tightness and realized her mistake. She was rushed to a nearby emergency room and was treated for 2½ hours with epinephrine, corticosteroids, aminophylline, and IPPB therapy. In April, 1971, because of the question of asthma associated with acetaminophen ingestion, an acetaminophen challenge was carried out and was negative (Fig. 2). Bronchial inhalation challenge was carried out in June, 1971, to determine if the previously demonstrated SSA might be playing a perpetuating role in her asthma. Successive inhalation challenges with increasing concentrations of Bermuda grass extract (SSA present) resulted in a 45 per cent fall in the FEV₁ from base-line determinations (Fig. 3). Induced bronchospasm was not accompanied by conjunctival, nasal, or cutaneous symptoms and was rapidly reversed by one isoproterenol IPPB treatment. On another day, a control challenge with Johnson grass was carried out (no SSA against Johnson grass), and the FEV₁ did not change. Bermuda grass immunotherapy was initiated. Her asthma has remained under control with the use of alternate-day prednisone therapy.

Case 2

N. F., a 37-year-old woman, gave a one year history of constant nasal stuffiness, post-nasal drip, and asthma. Her prior physician had discovered positive immediate wheal and flare skin test responses and treated her with an allergy elimination diet, twice-weekly allergy injections, and standard bronchodilators without glucocorticoid drugs. On this regimen her asthma became progressively worse. She denied an association between aspirin ingestion and asthma episodes. Physical examination revealed pink, congested nasal mucosa without polyps. The chest was filled with wheezes and rhonchi. The timed vital capacity (TVC)

TABLE IV. Positive aspirin challenge in Patient N. F.

Time	TVC	FEV ₁	Clinical
			Ingested prednisone 10 mg. and Tedral one hour before challenge
0	4,100 c.c.	2,650 c.c.	Chest clear, no rhinorrhea
	Aspirin 10 grains was given by mouth in form of Ascriptin		(acetylsalicylic acid content unknown to patient)
30 min.	4,000 c.c.	2,500 c.c.	Chest clear
45 min.	1,450 c.c.	600 c.c.	Severe asthma, rhinorrhea, conjunctival injection
	R: epinephrine, intravenous aminophylline, methylprednisolone, IPPB with isoproterenol		Patient's condition gradually improved
1½ hours	2,800 c.c.	1,200 c.c.	Patient very tired
4 hours	3,425 c.c.	1,625 c.c.	Patient very tired

was 1,000 c.c., FEV₁ was 600 c.c., and a maximum midexpiratory flow (MMEF) rate was 0.15 L. per second. Both maxillary sinuses were opacified on roentgenograms. After intensive inpatient treatment, the FEV₁ increased to 2,350 c.c. The presence of SSA was confirmed. Left maxillary sinus aspirate grew out *Pseudomonas fluorescens* on culture. Aspirin challenge was positive, as outlined in Table IV. Bronchial inhalation challenges to house dust and desert ragweed (SSA to both allergens) were negative. Asthma was controlled with oral bronchodilators and alternate-day prednisone. Sinus infection was treated with aspiration, antibiotics, and, eventually, antrostomies. Tartrazine (25 mg.) and acetaminophen (640 mg.) challenges were negative.

Case 3

W. R. a 56-year-old man, was first seen in June, 1971, for evaluation of persistent asthma. At age 20 he developed typical August and September hay fever symptoms while residing in Chicago. His hay fever was mild, easily controlled with antihistamines and not associated with asthma. In April, 1971, he developed an evening cough. The diagnosis of "allergic bronchitis" was made, and he was treated with triamcinolone, chlorpheniramine, and ascorbic acid (Aristomin). In March, 1971, because of constant cough and wheezing, he traveled abroad where treatments with synthetic ACTH injections resulted in dramatic correction of his bronchial symptoms. After returning to the United States he became severely dyspneic and sought further attention at Scripps Clinic and Research Foundation. He had no recent history of nasal congestion, paranasal sinus pain, or postnasal drip. Although he rarely ingested aspirin tablets, he did not recall associated asthmatic symptoms. On physical examination he was in moderately severe respiratory distress and had a cough productive of yellow phlegm. The nasal examination revealed no polyps or pus. The maxillary sinuses did not transilluminate. On auscultation, the chest was filled with inspiratory and expiratory wheezes and rhonchi. An FEV₁ of 1,300 c.c. rose to 1,700 c.c. after isoproterenol inhalation. Sinus x-rays showed bilateral maxillary sinus opacification. Skin tests to common inhalant allergens, including ragweed, were negative. An otorhinolaryngologist aspirated pus from the left antrum, and the culture grew nonhemolytic staphylococci. Intravenous fluids, corticosteroids, aminophylline, and antibiotics were administered, and bilateral antrostomies were performed. After 2 weeks, his symptoms had cleared, FEV₁ had increased to 3,700 c.c., and he was receiving alternate-day prednisone therapy. An aspirin challenge was negative and was performed on a day when he was not receiving prednisone. Since July, 1971, his asthma has been well controlled on a program of bronchodilators and alternate-day prednisone. In November, 1971, he experienced increasing nasal congestion and postnasal drip. His maxillary antra were now filled with

polyps. A bilateral Caldwell-Luc procedure was carried out. Repeat aspirin challenge was negative.

DISCUSSION

The incidence of aspirin intolerance in bronchial asthma is unknown. Previous estimates have varied by 100-fold, depending in part on the population sampled and the means of determining intolerance. Gardner and Blanton¹⁹ polled their fellow allergists and arrived at an incidence of 0.2 per cent aspirin intolerance in the asthma population. Farr¹³ noted an incidence of 20 per cent in the severe, adult, asthmatic patients admitted to the National Jewish Hospital. Some of these patients were not aware of their intolerance until challenged with aspirin. Van Leeuwen¹⁶ found an incidence of 16 per cent in a group of severe asthmatic patients but felt that in a general asthmatic population the incidence would be closer to 10 per cent. Other incidence estimates have been reported by Walton and Randle¹⁸ (3.2 per cent) and Giraldo and associates¹⁰ (3 and 5.6 per cent in two separate populations).

The incidence of aspirin intolerance in our asthmatic population is probably greater than the 8 per cent listed in Table I. Only 42 patients were challenged, leaving untested 38 other patients with two or more hallmarks of the aspirin syndrome and 100 patients with at least one such hallmark. We estimate the incidence of aspirin intolerance in our asthma population to be between 10 and 16 per cent.

Aspirin challenge in this study appears to identify a group of aspirin-intolerant patients whose onset of asthma following aspirin ingestion is usually delayed and perhaps relatively mild. The earliest onset of symptoms in patients with a positive aspirin challenge was 45 minutes, while several patients with a positive history described symptoms within 10 to 20 minutes. We suspect that those patients whose symptoms begin longer than 30 minutes after aspirin ingestion are less able to correlate aspirin intake with aggravation of asthma, particularly if constant asthma characterizes their clinical course. Some patients have a negative history of aspirin intolerance because aspirin has not been recently ingested.

Previous clinical characterizations of the aspirin-intolerant asthma population have stressed the associated findings of nasal polyps and sinusitis.¹⁰⁻¹² We also noted these hallmarks in most of our aspirin-intolerant patients (Table III). However, one of the 14 patients who gave a history of aspirin intolerance had none of the hallmarks. Many asthmatic patients who were not aspirin intolerant possessed these hallmarks. Patient W. R. had three hallmarks of the aspirin-intolerant syndrome, but his aspirin challenge was negative. Thus, while these hallmarks identify a potential aspirin-intolerant population, they cannot be identified except by aspirin challenge unless the patients give a history of aspirin intolerance.

We would also emphasize the frequent requirement for maintenance corticosteroids in our aspirin-intolerant patients. Sympathomimetic and xanthine drugs are usually insufficient in controlling constant asthma, which often responds to maintenance corticosteroids. All but 2 (91 per cent) of our aspirin-intolerant

patients were receiving maintenance corticosteroids. Attempts to discontinue corticosteroid treatment in our aspirin-intolerant patients have been generally unsuccessful, but the patients are often asymptomatic while taking low-dose alternate-day prednisone. It is our impression that treatment of upper airway diseases, including polypectomies, sinus irrigations, appropriate antibiotics, and early antrostomies, may be associated with improved asthma control. We have not noted worsening of asthma during or after polypectomy in any of our patients, although this has been reported by others.^{9, 12} Previous characterizations have minimized the importance of SSA to inhalant allergens in aspirin-intolerant asthmatic patients. Samter and Beers¹² found positive skin test reactions to seasonal and environmental inhalant allergens in only 10 per cent of their patients. In our aspirin-intolerant patients, however, the incidence of SSA (68 per cent) was similar to that of the general asthma population (73 per cent). As demonstrated by Patients G. J. and N. F., SSA may or may not reflect bronchial reactivity to inhalation of the same antigens. When possible, we have used bronchial inhalation challenge as a guide to initiating immunotherapy in our aspirin-intolerant patients, but this experience is too limited to permit conclusions about the incidence of positive bronchial inhalation challenges in these individuals.

Patients who are intolerant to aspirin also have been found to be intolerant to a variety of other drugs and chemicals. Demonstration of intolerance to aspirin should lead to consideration of intolerance to these substances. The association of the ingestion of indomethacin, aminopyrine, and tartrazine with attacks of wheezing was reported by Samter and Beers.¹² Chafee and Settippane²⁰ reported a patient with intolerance to tartrazine.²⁰ More recently, cross-intolerance with acetaminophen, mefenamic acid, and dextropropoxyphene has also been reported.²¹ It seems important to select analgesics which have rarely or never been reported to precipitate asthma (sodium salicylate, acetaminophen). Whenever possible, the initial ingestion of a new analgesic should take place under medical observation. If there is an equivocal history of intolerance, such as reported by Patient G. J., to the drug acetaminophen, oral challenge, similar to that described for aspirin, is an effective way to settle the question (Fig. 2).

We wish to emphasize again that aspirin challenges should not be performed on patients with a clear history of aspirin intolerance. Furthermore, we recognize the risks involved in administering aspirin to asthma patients whose response to aspirin is unknown. The procedure should be done under close supervision, with all inpatient treatment modalities available. In our institution, inpatient facilities, including an intensive-care unit, are adjacent to our Allergy Clinic. It does not seem appropriate to conduct aspirin challenges away from the hospital complex. Even though severe asthma and death have followed aspirin ingestion, no life-threatening emergencies arose in our series. However, the use of medications which contain aspirin is so common that most people can be expected to ingest aspirin during their lifetime. One can argue that it is safer to have aspirin reactions occur in a controlled medical environment rather than in the patient's home. Our method of challenging asthma patients with usual therapeutic doses of aspirin (640 mg.) has satisfied our objective of safety and accurate discrimination. Perhaps the prior administration of mainte-

nance bronchodilators, including corticosteroids, protects our patients from more violent reactions to aspirin in some cases. Conceivably, usual maintenance medications may mask or prevent minimal airway responses to aspirin, producing some false negative challenges. However, the advantages of achieving stable FEV₁ values during a 4 hour challenge procedure justifies pretreatment with the patient's usual bronchodilators. Other procedures for challenging patients with smaller test doses of aspirin have been advocated.²² Further experience will be needed to determine which is the optimum test procedure. For the present it seems prudent to advise *all* asthmatic patients to avoid aspirin and aspirin-containing products unless they are known to be aspirin tolerant. Oral challenge testing should be employed only by physicians experienced in the management of acute, severe asthma working in an environment in which all inpatient treatment modalities are immediately available.

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