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Intolerance to Aspirin

Clinical Studies and Consideration of its Pathogenesis

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SUMMARY Angioedema and rhinitis, nasal polyposis, and bronchial asthma of aspirin-sensitive patients are acquired diseases that develop, as a rule, after middle age in predominantly nonatopic patients. In many instances, nasal and bronchial symptoms precede the development of intolerance to aspirin by months or even by years. Salicylates other than acetylsalicylic acid fail to produce symptoms in aspirin-sensitive patients. Exposure to several chemicals, on the other hand, that are structurally unrelated to aspirin can induce comparable "aspirin-like" symptoms. The structural dissimilarity of these compounds is so pronounced that immunological cross-reactivity appears most unlikely. The substances that have been found to induce aspirin-like symptoms have one characteristic in common—they are strong minor analgesics and include pyrazolones and indomethacin as well as aspirin. Peripheral analgesics might act on peripheral chemoreceptors and initiate a series of reflexes that might produce either angioedema, or rhinitis and bronchial asthma, or all of these.

INTOLERANCE TO ASPIRIN has been known for more than 50 years. The first description, by Hirschberg (1), appeared only 3 years after the synthesis of the drug. Van Leeuwen (2) discussed its clinical significance in 1928. Several reports of death after ingestion of aspirin have appeared in the

literature (3, 4). Cooke (5) tested 3 of 9 aspirin-sensitive patients with salicylic acid, benzoic acid, antipyrine, sodium acetate, and methyl salicylate and noted the absence of untoward reactions. Prickman and Buchstein (6) analyzed the histories of 62 (40 female and 22 male) aspirin-sensitive patients: 4 had sinusitis; 11, hay fever; 21, vasomotor rhinitis and nasal polyps; and 43, asthma. Migraine occurred in 6 and urticaria (or angioneurotic edema) in 10 of their patients. As early as 1929, Francis (7) emphasized the risk of polypectomy precipitating bronchial asthma in the "aspirin-sensitive" patient.

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TABLE 1. Clinical Features of 182
Aspirin-Sensitive Patients

Data	No. of Patients
Sex: male	78
female	104
Onset before age 30	46
Duration of aspirin sensitivity:	
less than 5 years	70
more than 5 years	112
Respiratory symptoms only	154
Angioneurotic edema and urticaria only	18
Respiratory symptoms and urticaria	10
Family history of atopy	40
Positive skin reactions to seasonal and environmental inhalant allergens	19
Nasal and paranasal polyps	92
Polypectomies	72
First attack of bronchial asthma within 9 months after polypectomy	18
Bronchial asthma aggravated by polypectomy	30
Associated sensitivities	42*

* See breakdown in Table 2.

Gardner and Blanton (8) made an attempt to determine the prevalence of aspirin sensitivity in 467 patients—more than one half, asthmatics—and found only 5 patients who reported symptoms when asked: "Do you take aspirin?" and "What effect have you noticed from it?" They also polled a group of allergists about their experience with aspirin-sensitive patients: The returned questionnaires yielded a calculated prevalence of 0.2% which, we believe, is lower than the true prevalence of the disease.

Our studies, which are summarized in this report, indicate that intolerance to aspirin is reasonably common; that the evidence for an "allergic" response to aspirin, that is, for the formation of antibodies as a cause of this intolerance, is inconclusive; that the clinical triad of nasal polyposis, bronchial asthma, and life-threatening reactions to acetylsalicylic acid is a disease

entity, not a chance cluster of allergic symptoms, and represents, in fact, the prototype of a syndrome that has not been previously described and deserves recognition.

THE NATURAL HISTORY OF INTOLERANCE TO ASPIRIN

From 1954 to 1965, we have followed more than 1,000 "aspirin-sensitive" patients. In the beginning, new patients returned to the Allergy Clinic at weekly intervals for extensive studies and long-term observation in order to clarify the natural history of the disease and permit adequate classification. Since 1959 we have carried out prospective studies on 182 patients who were admitted to the medical wards of the University of Illinois Research and Educational Hospitals. Our conclusions are based upon our findings in this latter group of patients: Table 1 lists their essential clinical characteristics.

Onset and progression of the changes in skin and respiratory tract which are associated with intolerance to aspirin occur in a pattern that can be uncovered by history or observation in more than 80% of our patients, although Table 1 makes it evident that every patient does not necessarily present every potential component of the syndrome. Childhood, adolescence, and the beginning of adult life are not distinguished by any particular disease. During the second or third decade of life an intermittent "vasomotor rhinitis" develops in patients of either sex that is distinguished by profuse watery secretions and eventually followed by chronic nasal blockade and loss of intermittency.

The swelling of the nasal mucous membrane tends to become continuous and responds less and less to vasoconstrictors. Nasal and paranasal polyps develop: 92 out of 182 of our "respiratory" patients had nasal polyps. Polyps tend to be bilateral and respond poorly to therapy. Sixty-eight patients had multiple polypectomies, some as often as once a month: Polypectomy

does not control the tendency of the polyps to re-form.

The first episode of bronchial asthma is rarely related to a well-defined precipitating factor, but onset or aggravation of bronchial asthma follows nasal polypectomy in a suggestive number of patients.

Bronchial asthma in aspirin-sensitive patients occurs, as a rule, in middle age. Previous papers—for instance, Leigh and Rawnsley's review (9) of bronchial asthma of late onset—suggest "that emotional precipitants are of notable importance in late onset asthma and that they are, perhaps, rather more important in the etiological complex of late onset asthma than of asthma originating in earlier life." Similarly, Rees (10) suspects that a special personality type predisposes to "intrinsic" bronchial asthma. We noted the common presence of great anxiety that appears to be associated with obstructive pulmonary disease of older patients (11), but we did not recognize any specificity.

During the initial stage, bronchial asthma of aspirin-sensitive patients is distinguished by [1] its impressive reversibility with bronchodilators and [2] by its response to maintenance doses of corticosteroids that are considerably smaller than the doses required for the control of immunologically induced bronchial asthma of comparable severity.

Nasal polyposis and bronchial asthma continue whether or not aspirin is ingested. Moreover, the first aspirin-induced reaction may not occur until respiratory manifestations of the disease have been present for years.

Bronchial asthma in aspirin-sensitive patients has been held to be severe, if not intractable (12). While it is true that some of our patients (26 of 182) showed progression, documented by ventilatory function tests during the period of observation, a surprising number of aspirin-sensitive patients—including patients who have suffered severely during the early stages of

the disease—may improve; and a few of our patients (16 of 182) have become free of asthma unless attacks are precipitated by aspirin. It is interesting, however, that no patient under our care has ceased to form nasal polyps once the presence of polyps had been established.

Since many of our patients had taken aspirin in the past with impunity, the initial reaction is usually unexpected and, in fact, quite often not attributed to the drug.

No correlation exists between the frequency with which patients have taken aspirin in the past and the severity of their reactions. By and large, the severity of the reaction is a function of a host and tends to remain the same. It is our impression, however, that patients who have noted comparatively mild reactions to aspirin but have avoided it faithfully for many years might have more severe reactions to the drug after a long and comparatively symptom-free interval.

Patients who are sensitive to aspirin suffer from respiratory symptoms, or urticaria, or both. Once they occur in a given tissue, reactions to aspirin are remarkably similar in quality but differ in quantity. The natural history—date of onset, severity of reaction, and progressiveness—varies from patient to patient. Urticaria, for instance, might occur only after ingestion of aspirin or may persist even though aspirin is avoided.

ATOPY AND ASPIRIN SENSITIVITY

The incidence of atopy in our group of patients is low. Each patient was carefully screened for signs of atopic sensitivity before hospitalization. Screening included skin tests to seasonal and environmental inhalants and to suspected foods. Atopy was assumed to exist when two of the following three criteria were fulfilled: [1] a positive family history of atopy; [2] an established correlation between exposure to an atopic antigen (allergen) and subsequent

development of clinical symptoms, regardless of skin tests; and [3] unequivocal positive skin reactions to atopic antigens to which the patient had been exposed, regardless of symptoms. Compared with an expected prevalence of up to 20% in a random population (13, 14), the aspirin-sensitive group has an incidence of atopy of less than 3%. A significant number of our patients, on the other hand, have a family history of atopy; 46 of 182 patients have children with confirmed allergic manifestations.

In the occasional patient who is clearly atopic before "aspirin sensitivity" develops, the clinical picture is not that of an atopic person who has simply acquired a new sensitivity. Without exception, the whole clinical syndrome shifts from intermittent symptoms, with usually clear-cut cause-and-effect correlation, to perennial symptoms without a pattern that can be recognized. For a brief time the previously identified allergens might continue to produce exacerbations of symptoms during exposure, but this changes rapidly. Clinical sensitivity to the previously significant allergens is lost—it is as though an entirely new, more profound disease has superseded the primary atopic state.

Serial throat and sputum cultures established that bacterial infection was of only minor significance in our series of patients. Pathogens were found less frequently (1:3) than in throat and sputum cultures, obtained during identical seasons, of non-selected asthmatic patients with cases of equal severity. We cannot state that initial infection does not play a role in bringing about the changes in skin and mucous membranes which eventually render them sensitive to aspirin, but we can state that extensive surgery of the nose and paranasal sinuses, carried out in eight of our patients before admission—Caldwell-Luc operation to remove foci of infection and establish better drainage—failed to alter the natural history of the disease.

THE REVERSIBILITY OF ASPIRIN-SENSITIVE BRONCHIAL ASTHMA

The respiratory tract of aspirin-sensitive patients does not present any unique functional behavior. Like patients with other forms of "intrinsic" bronchial asthma, aspirin-sensitive asthmatics are sensitive to intravenous administration of histamine and methacholine (Mechohyl®) (15). Particularly during the early stages of the disease, bronchial asthma of aspirin-sensitive patients responds readily to bronchodilators.

The reversibility of the early bronchial asthma of aspirin-sensitive patients is impressive. It seemed to us that it might be the bronchial equivalent of the initial intermittent rhinorrhea and might provide a clue as to the pathogenesis of the syndrome.

An attempt was made to compare the effect of histamine and methacholine on the vital capacity of aspirin-sensitive (nonatopic) asthmatics and non-aspirin-sensitive (clearly atopic) asthmatics of comparable severity. We infused methacholine chloride and histamine phosphate intravenously under electrocardiographic control and determined the amount required to induce a 40% reduction in the 1-sec vital capacity. Methacholine chloride was given in increments of 25 μ g, histamine, of 10 μ g (of histamine base). The results are summarized in Tables 3 and 4: The amounts of the drugs required to produce a 40% reduction in vital capacity in asthmatics with aspirin intolerance are significantly less (histamine, $P < 0.001$; methacholine, $P < 0.05$) than those in a similar group of non-aspirin-sensitive patients with bronchial asthma of equal severity. In fact, it was not possible to achieve a 40% reduction in 1-sec vital capacity in the majority of the "allergic" patients, because side effects—that is, violent headache after injection of histamine and first-degree heart block after injection of methacholine—made it necessary to discontinue the infusion before the end point was reached. Once, methacholine chloride produced rather severe bronchial asthma that was rapidly terminated by intravenous injection of atropine sulfate.

While acetylsalicylic acid is outstanding in its ability to precipitate severe reactions, associated idiosyncrasies occur and are listed in Table 2. Of foods that were impli-

cated, fresh pork, sweet corn, soft drinks, and cheese crackers predominate. None of the patients who reported reactions after ingestion of food gave positive skin reactions to the food under suspicion. Analysis of the suspected foods established the presence of multiple additives in all but two of the samples. Of preservatives, sodium benzoate was used most commonly; of coloring matter, hydrazine yellow—"tartrazine"—(Food, Drug, and Cosmetic yellow no. 5) turned out to be a component of all but one of the yellows in orange foods. The ability of hydrazine yellow to induce angioedema and respiratory symptoms in susceptible patients has been previously described (16, 17), but it had not been shown that reactions to hydrazine yellow and to aspirin coexist in the same patients: Figure 1 shows the structure of hydrazine yellow and of its metabolites (18).

The incidence of penicillin and sulfonamide sensitivity in this group is probably not any higher than in a random population, but morphine, morphine derivatives, and codeine produce striking and severe reactions in a limited number of patients. Reactions to aminopyrine and antipyrine—

TABLE 2. Associated Sensitivities in 182 Aspirin-Sensitive Patients

Sensitivities to:	No. of Patients
Foods	26
Alcohol (in various forms)	14
Tartrazine (Food, Drug, and Cosmetic yellow no. 5)	14
Seasonal and/or environmental inhalants	10
Perfumes and odors	12
Drugs	
Penicillin	11
Morphine, morphine derivatives, codeine	16
Antipyrine and aminopyrine	4
-caine compounds	5
Sulfonamides	3
Isoniazid	1

which are not commonly used at present—are comparatively rare but, if they occur, resemble reactions produced by acetylsalicylic acid.

SPECIFICITY OF INTOLERANCE TO ACETYLSALICYLIC ACID

The assumption that patients who cannot take aspirin are allergic to it is probably due to the peculiar features of the

TABLE 3. Amounts of Histamine and Methacholine Required to Induce a 40% Drop in Vital Capacity in 11 Non-Aspirin-Sensitive Patients Suffering from Bronchial Asthma

Name	Sex	Age	Weight	Basal Vital Capacity		Histamine		Methacholine	
				1-sec	Total	Absolute	Per Kilogram	Absolute	Per Kilogram
		yr	kg	liters		μg		μg	
L. P.	M	40	52.3	1.60	2.00	100*	1.91	520	9.94
H. Z.	F	37	59.1	1.20	1.25	100*	1.69	400†	6.76
B. W.	F	50	50	1.00	1.20	10	0.20	75	1.50
R. T.	F	46	68.2	1.20	1.85	100*	1.46	350†	5.13
L. M.	F	13	55.5	2.0	2.90	70*	1.26	250†	4.50
P. S.	F	50	61.8	1.7	3.10	20	0.29	270†	4.36
C. U.	F	45	59.1	2.00	2.15	100*	1.69	250†	4.23
E. L.	M	35	91.8	1.40	1.45	100	1.08	450	4.90
V. Z.	F	33	56.8	2.30	3.00	90*	1.58	400	7.05
J. A.	M	22	100	2.50	4.00	100	1.00	600	6.00
R. L.	M	22	81.8	5.00	5.40			350	4.27
						Mean = 1.22 μg/kg		Mean = 5.23 μg/kg	

* No effect on vital capacity—titration terminated because of violent headache.

† No effect on vital capacity—titration terminated because of heart block.

TABLE 4. Amounts of Histamine and Methacholine Required to Induce a 40% Drop in Vital Capacity in 11 Aspirin-Sensitive Patients Suffering from Bronchial Asthma

Name	Sex	Age	Weight	Basal Vital Capacity		Histamine		Methacholine	
				1-sec	Total	Abso- lute	Per Kilogram	Abso- lute	Per Kilogram
		yr	kg	liters		μ g		μ g	
M. F.	F	62	86.4	1.10	2.20	20	0.23	250	2.77
J. J.	M	59	58.7	1.20	1.80	10	0.17	200	3.49
V. P.	F	45	65.9	1.50	1.90	30	0.45	240	3.49
F. P.	M	40	86.5	2.40	3.40	45	0.52	250	2.89
V. P.	F	47	70.5	1.40	2.20	10	0.14	100	1.42
J. S.	M	24	63.6	3.30	3.70	25	0.39	200	3.14
S. T.	M	41	65	2.90	3.50	50	0.76	400	6.15
V. G.	F	19	47.7	1.60	3.00	35	0.73	200	4.19
G. B.	M	47	99	2.90	4.25	20	0.20	300	3.03
E. P.	M	49	54.5	2.80	3.80	20	0.36	350	6.42
F. J.	M	51	75.7	0.95	2.30			250	2.91

Mean = 0.39 μ g/kg Mean = 3.63 μ g/kg

syndrome: The explosiveness of the reactions makes it attractive to compare the syndrome with anaphylaxis, which is similarly explosive.

It is interesting that a significant number of patients were not aware at the time of their admission that they were sensitive to aspirin and had to be given aspirin as part of their clinical survey. The decision to establish aspirin sensitivity by actual exposure was not made lightly. It requires anticipation of severe angioedema, bronchial asthma, cyanosis, asphyxia, and, possibly, coma, and should not be undertaken unless an anesthesia team is present to maintain open airways if necessary. On the other hand, it is obviously safer to administer aspirin to patients with suspected intolerance under controlled hospital conditions than to take a chance that they might obtain it, in one of many proprietary preparations, on the outside; but while safer, it is not safe.

Thirty-six patients who maintained that they could take aspirin without ill effects were given 0.3 g of acetylsalicylic acid: 34 developed reactions. Symptoms may appear almost at once; they begin in most patients within 20 min but occasionally

after an interval of up to 2 hr. The onset of the reaction is marked by profuse watery rhinorrhea and, often, by a vivid scarlet flush of head, neck, upper chest, and extremities. At times, the initial reaction is followed by nausea, vomiting, intestinal cramps, and diarrhea. Bronchoconstriction, wheezing (without impressive cough), and cyanosis occur, as a rule, within a few minutes after the nasal symptoms.

Pretreatment with corticosteroids did not prevent aspirin-induced bronchial asthma, but corticosteroids administered after the onset of symptoms seemed to shorten the period of recovery; the evaluation of their effectiveness is difficult, however, since they were used only in patients who failed to respond to nonsteroid therapy. As a rule, epinephrine (aqueous, 1:1,000, 0.4 ml intramuscularly) and aminophylline are sufficient to control reactions. Aminophylline is the drug of choice but must be given by syringe (500 mg in 20 ml, injected slowly), followed by intravenous infusion (500 mg in 250 ml 5% glucose, every 4 to 6 hr). Neither epinephrine nor aminophylline had any apparent effect on the rhinorrhea or on the cutaneous flush. Most patients recover from acute reaction within 2 hr, but a general feeling of malaise and excessive bronchial secretion might persist for several days. We induced several episodes but did not encounter shock or fatalities.

34/36
pt -
2 reacted
to 300mg
of ASA

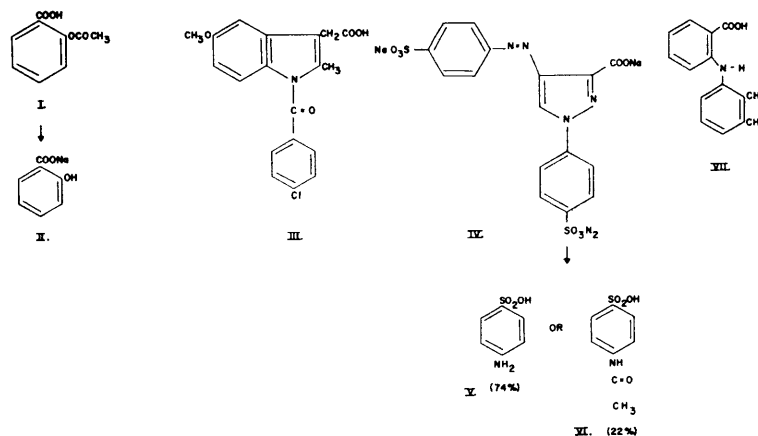


FIGURE 1. I. Acetylsalicylic acid. II. Sodium salicylate. III. Indomethacin. IV. Tartrazine (hydrazine yellow = Food, Drug, and Cosmetic yellow no. 5). V. Sulfanilic acid. VI. p-acetamidobenzenesulfonic acid. VII. Mefenamic acid. Compounds I, III, and IV induce reactions in aspirin-sensitive patients; compounds II, V, and VI are innocuous; compound VII is suspected.

Regardless of history, each of the 182 aspirin-sensitive patients was given, in rotation, at least 1 of the following drugs: [1] sodium salicylate, [2] salicylic acid esters with lengthening side chain in the ortho-position, [3] choline salicylate, [4] thioaspirin, and [5] N acetyl-p-aminophenol. Considering multiple tests, each drug was taken by 40 aspirin-sensitive patients: No untoward reactions occurred.

It is certain that intolerance to acetylsalicylic acid is not an intolerance to salicylates. Aspirin, however, is not the only chemical that causes symptoms in the skin and respiratory tract of aspirin-sensitive patients. We have previously mentioned that tartrazine is poorly tolerated by a significant number of patients who cannot tolerate aspirin. Recently, we observed that indomethacin—an indole derivative which has no structural relationship to acetylsalicylic acid—induces severe “aspirin-like” reactions in aspirin-sensitive patients. Since then we have confirmed this coexisting intolerance in 18 hospitalized patients who developed intense broncho-obstructive

and there is no reason to assume that they had an opportunity to develop a preexisting immunological sensitivity to the drug (19).

It should be noted that aspirin and indomethacin are effective minor analgesics, and the structural relationship between hydrazine yellow and aminopyrine is evident (Figure 1). In fact, it would not be surprising if hydrazine yellow—given in adequate doses—would turn out to provide effective relief for peripheral pain. By the same token, it is almost certain that the mode of action of one of the recently synthesized minor analgesics, mefenamic acid (Figure 1), is so similar to the mode of action of aspirin that it must be expected to produce aspirin-like reactions in aspirin-sensitive patients.

NONIMMUNOLOGICAL FACTORS IN THE PATHOGENESIS OF BRONCHIAL ASTHMA

Several investigators have suggested that bronchial asthma cannot be explained by an immunological sequence alone but might be associated with abnormal autonomic controls. Enninger and Hess (20), Na-

"vagotonic disease." More recently, an inadequacy of the beta-adrenergic-bronchodilator—receptors of the bronchial mucous membrane has been suggested as a possible explanation for the nonspecificity of bronchial asthma (23, 24). Neither sympathetic nor parasympathetic receptors, however, appear to participate in the pathogenesis of the bronchial asthma of aspirin-sensitive patients.

Even extrinsic bronchial asthma is a disease of multiple factors. The search for significant mediators of the immunological sequence, for instance, has yielded significant new information, but it is rarely certain which of the substances that have been identified—for example, histamine or the slow-reacting substance of anaphylaxis (SRS-A) (25)—accounts for the clinical symptoms in the individual patient. Patients who suffer from aspirin-sensitive bronchial asthma are more closely "intrinsic" (to use Rackemann's terminology (26)) than in any other type of bronchial asthma (27, 28): More than 60% of our patients listed sensory stimuli, for example, exposure to draft, change in weather, contact with fumes and odors, as precipitating factors.

The clinical course of "extrinsic" bronchial asthma reflects the patient's exposure to inhalant allergens even though the severity of the symptoms might vary from patient to patient or within the same patient from season to season: The aspirin-sensitive patient, on the other hand, has "intrinsic" symptoms that occur "without rhyme or reason" (to use an expression that aspirin-sensitive patients seem to favor) and that are not correlated with seasonal or environmental exposure to allergens.

If the respiratory symptoms that precede the development of intolerance to aspirin in aspirin-sensitive patients are not the result of an immunological sequence, they must be due to the action of nonimmunological mediators or chemoreceptors that can cause vasodilation, secretion of mucus,

and bronchoconstriction. The analysis of our findings has led us to conclude that rhinitis and bronchial asthma of aspirin-sensitive patients are initiated by peripheral chemoreceptors that had not been known to participate in the control of respiration. It is likely that these receptors are kinin receptors since kinins—for example, the nonapeptide, bradykinin—have been identified in recent years as mediators of noxious stimuli in skin and respiratory membranes (29–31). Receptors that are stimulated by kinins may initiate an axon reflex, that is, wholly peripheral vascular response, or transmit stimuli to the dorsal root ganglion and beyond.

Our observations suggest an unusual responsiveness of the chemoreceptors of the nasal and bronchial mucous membranes of aspirin-sensitive patients. Unusual responsiveness alone, however, does not explain the unusual effect of aspirin on the skin and the respiratory tracts of these patients. Recent studies have clearly established that aspirin is an antagonist of bradykinin (32, 33). In aspirin-sensitive patients, on the other hand, it has a paradoxical effect that we attribute to a preexisting injury of the chemoreceptors in skin, or mucous membranes, or both (19): The antagonist has become an agonist and produces the stimuli that it ordinarily prevents.

If our interpretation is correct, it may become understandable why other analgesics which, like pyrazolones and indomethacin, act on the same receptors, induce comparable reactions.

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