

Oral aspirin challenges in asthmatic patients: a study of plasma histamine

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Summary

Under carefully controlled conditions, seven aspirin-intolerant asthmatic patients were challenged with oral aspirin and experienced respiratory tract reactions with a decline in forced expiratory volume in 1 sec (FEV₁), ranging from 26 to 64%. Venous blood samples, which were collected during the challenges, showed a rise in plasma histamine in all seven patients. The increase in plasma histamine occurred at the onset of their respiratory reactions and those patients with the most severe asthmatic responses were found to have the highest and most prolonged levels of plasma histamine. The same aspirin-intolerant asthmatic patients were able to ingest Maalox® or sodium salicylate without untoward effects, decline in FEV₁ values or changes in plasma histamine levels. Ten non-asthmatic individuals and eight out of ten asthmatic control patients were able to ingest aspirin without any reactions or changes in their plasma histamine levels. However, two asthmatic control individuals, with severe asthma requiring treatment with moderate dosages of corticosteroids, were found to have elevated pre-challenge plasma histamine levels which increased during their ASA challenges despite the absence of respiratory reactions or changes in FEV₁ values. It is possible that these two individuals were unsuspected aspirin-intolerant asthmatics. These studies demonstrate that asthmatic reactions to acetylsalicylates are associated with release of histamine into plasma in the subgroup of asthmatic patients with the aspirin-intolerance syndrome. Such a finding suggests that histamine may be one of the mediators of bronchospasm in aspirin-induced asthma.

Introduction

Hirschberg (1902) was the first to describe untoward reactions to aspirin (ASA). Since then, clinical descriptions have focused upon respiratory tract reactions to ASA, such as rhinoconjunctivitis and bronchospasm (Vander Veer, 1920), or urticarial reactions to ASA (Moore-Robinson & Warin, 1967). On the basis of clinical and laboratory observations and the perseverance of Samter and Beers (1967), most investigators now agree that the asthmatic reactions to aspirin are probably not

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mediated by specific reaginic antibodies against ASA, whereas some urticaria-angioedema reactions to aspirin are probably mediated by such antibodies (De Weck, 1971). The asthmatic reactions which aspirin-intolerant asthmatics experience after ingesting aspirin are probably non-immunological because: (a) these patients have cross-intolerance to a wide spectrum of drugs which are antigenically distinct from ASA (Smith, 1971; Vanselow & Smith, 1967); (b) their reactions frequently occur upon first exposure to the above drugs (Samter & Beers, 1968); (c) they lack cross-intolerance to other salicylates, such as sodium salicylate, which theoretically should cross-react if immune specificity were important (Samter & Beers, 1968); (d) it has not been possible to detect anti-ASA reaginic antibodies by direct cutaneous testing (Matthews, Lovell & Sheldon, 1950), or by passive transfer studies to monkeys (Schlumberger, Löbbecke & Kallos; 1974); (e) the identification of other classes of anti-ASA or anti-acetylated protein antibodies has not been limited to the sera of aspirin-intolerant asthmatic patients and has not been a consistent finding in these patients (Pinckard, Hawkins & Farr, 1968; Yurchak, Wicher & Arbesman, 1970); (f) attempts to produce anaphylactic reactions in monkeys given ASA orally after intravenous passive transfer of sera from known ASA intolerant asthmatic patients have failed (Vantansuk, Hornbrook & Kohler, 1971).

Samter (1973) stated that the aspirin-induced asthmatic reaction is the most dramatic feature of a systemic disease, which continues between exposures to ASA and may be a basic connective tissue defect, possibly aggravated by acetylation. Schlumberger *et al.* (1974) have suggested that the asthmatic reaction to aspirin results from direct (i.e. not antibody mediated) liberation of histamine and other mediators by drug interactions with tissues containing mediator stores.

In the study reported in this paper, plasma histamine was found to be increased during asthmatic reactions produced by ASA ingestion in asthmatic patients known to be intolerant of ASA.

Materials and methods

Subjects

Seven asthmatic individuals, four females and three males, ranging in age from 21 to 64 years, were selected for this study because they were known to have sustained mild to moderate asthmatic reactions to ASA by history or during previous ASA ingestion challenges (McDonald, Mathison & Stevenson, 1972). Patients who gave a history of a severe asthmatic response to ASA in the past were not invited to participate in this study. Details of the study and risks were carefully outlined for them and informed consent was obtained. Ten aspirin-tolerant asthmatic individuals served as one control group and ten non-asthmatic subjects whose lung function tests had not changed after inhaling methacholine (Mathison & Stevenson, 1973) served as the other control group.

At the time of the study, five out of seven aspirin-intolerant asthmatic patients were receiving oral bronchodilators (theophylline and ephedrine), three oral prednisone, one beclomethasone dipropionate by inhalation, one Decadron Turbinaire*, one cromolyn sodium, two were taking antihistamines and one colchicine. One patient (L.W.) was not taking medications. We selected the control group of aspirin-tolerant asthmatic patients at least in part because they were consuming approximately the same types and quantities of medications. Thus, of the ten aspirin-tolerant asthmatic

patients, six were taking prednisone, four theophylline, two oral metaproterenol, one beclomethasone dipropionate by inhalation and three individuals were not taking medications. The ten non-asthmatic individuals had not received medications immediately prior to or at the time of these challenge studies.

Aspirin challenges

ASA challenges were performed according to previously described methods (McDonald Mathison & Stevenson, 1972), except that the dosage of ASA was reduced to 325 mg in six of seven ASA intolerant patients and all of the control individuals. Forced expiratory volume in 1 sec (FEV_1) was used as the major indicator of increasing bronchial obstruction*. Most of the patients were hospitalized in the General Clinical Research Center during the study. On the first day, baseline pulmonary function values were obtained at 08.00, 12.00 and 18.00 hours. The patients' medications were noted and continued in their usual dosages. On the second day, one tablet of Maalox® (magnesium aluminum hydroxide 400 mg) was given as a control substance and venous blood samples were collected as indicated in the next section. On the third day, each patient's baseline pulmonary functions were obtained before and every 30 min after they ingested one tablet of Ascriptin® (ASA 325 mg and magnesium aluminum hydroxide 150 mg). Patient N.T. was given two tablets of Ascriptin®. If the patient developed chest tightness, flushing, rhinorrhea, nasal stuffiness, conjunctival symptoms or a greater than 20% decline in FEV_1 values, pulmonary function studies were obtained every 15 min until values returned to baseline levels. Significant bronchospasm was treated with aminophylline, epinephrine or inhaled isoproterenol as required. In addition, two of the aspirin-intolerant asthmatic subjects and one normal control individual were challenged with 325 mg of sodium salicylate on another occasion.

Method of blood sampling

During the experimental challenges with aspirin (Ascriptin®), Maalox® or sodium salicylate, an antecubital vein was cannulated with a #19 scalp vein needle and a continuous saline microdrip was infused between samplings. Blood samples were obtained before and after ingestion of aspirin or control substances at half-hourly intervals for 4 hr and then samples were collected at 8 and 24 hr. In addition, if adverse signs or symptoms were noted or when lung function declined significantly, in the ASA challenges only, blood samples were obtained at more frequent intervals (5, 10, 15, 30 and 60 min). At each sampling, 12 ml of blood was drawn into plastic syringes and part was transferred into a tube containing heparin which was used for cell counts and quantitation of plasma histamine in our Allergy and Immunology Laboratory. Serum samples were used to measure salicylate levels in the Clinical Pathology Laboratory.

Histamine assay

Plasma histamine was measured by the enzymatic isotopic technique as modified by Beaven, Jacobson & Horakova (1972). Briefly, this method involves conversion of histamine to 1-C14-methyl-4 (2-aminoethyl)-imidazole (C14 methyl histamine) by incubation with S-adenosyl methionine (C14 methyl) and a preparation of histamine-N-methyl-transferase from guinea-pig brain. The C14 methyl histamine was isolated

* Jones Pulmonor, Jones Medical Instruments Co., Oak Brook, Illinois.

by extraction into chloroform and the extracted radioactivity assayed by scintillation counting. Samples were assayed in duplicate and all samples from each patient's series of challenges were assayed at the same time. In our laboratory, this assay is sensitive and reproducible to values as low as 0.25 ng/ml of histamine.

Cell counts

Basophils and eosinophils were counted simultaneously after toluidine blue staining (Kimura, Moritani & Tanizaki, 1973).

Statistics

Statistical calculations were performed in a Compucorp 145-E statistician calculator (Computer Design Corporation, Los Angeles, California) utilizing chi-square with Yates correction factor to determine degrees of significance.

Results

Aspirin challenges

The results of acetyl salicylate challenges in aspirin intolerant asthmatic patients are presented in Table 1. The maximum salicylate levels in their sera ranged from 2.5 to 6.0 mg% (mean 4.1). These levels were detected at 31–180 min (mean 102.8) after aspirin ingestion. The maximum decline in their FEV₁ values ranged from 26 to 64% (mean 32.5) from the baseline. This degree of bronchial obstruction occurred 40–150 min (mean 95.1) after aspirin ingestion. For individual patients there was a close temporal relationship between maximum fall in FEV₁ and maximum salicylate level.

In addition to objective evidence of bronchial obstruction, as reflected in FEV₁ values, all aspirin-intolerant asthmatics developed subjective symptoms of chest tightness and either conjunctival or nasal congestion. Two patients experienced facial flushing. Patient N.T. had ocular symptoms and bronchospasm during the first challenge and one week later experienced only ocular symptoms during the second aspirin challenge. Urticaria or angioedema was not observed in these patients.

The changes in plasma histamine concentration after individual aspirin challenges are recorded in Table 1. All aspirin-intolerant asthmatic individuals released histamine into their venous plasma after aspirin ingestion. A representative patient (J.H.) who sustained a mild reaction to ASA is presented in Fig. 1. During her Maalox® challenge, there was no significant change in her FEV₁ values, serum salicylate levels or plasma histamine concentration during the 4 hr depicted in Fig. 1. Approximately 2 ng/ml of plasma histamine was detected before and during her control challenge. In contrast, 2 hr after ingesting ASA, the patient developed a mild respiratory reaction with ocular and nasal congestion, chest tightness and a 26% decline in FEV₁. This event coincided with a small rise in the serum salicylate level and a burst of histamine into her venous plasma (5.4 ng/ml) which returned to her baseline plasma histamine level of 2 ng/ml within 30 min. Histamine values obtained at 8 and 24 hr were also 2 ng/ml but are not shown in Fig 1.

In contrast to the mild reaction to ASA which is depicted in Fig. 1, a more severe asthmatic reaction occurred in patient N.F. and the chronological events are presented in Fig. 2. Thirty minutes after ingesting ASA, she developed facial flushing, intense rhinorrhea, wheezing and dyspnoea. Her FEV₁ fell 64% from the baseline value. This

Table 1. Serum salicylate levels, FEV₁, plasma histamine and clinical symptoms after oral aspirin challenges in seven aspirin (ASA)-intolerant asthmatic patients

Patient	Maximum salicylate level		Maximum decline FEV ₁		Histamine (ng/ml)		Clinical symptoms	Medications§
	mg%	Time*	Time*	% fall	B†	A‡		
1 L.W.	6.0	31	40	36	2.0	7.0	Rhinorrhea, dyspnoea, wheezing	None
2 N.F.	3.6	37	41	64	2.5	5.9	Facial flushing, rhinorrhea, wheezing, dyspnoea	Beclomethasone dipropionate (inhalation)
3 J.H.	2.5	120	120	26	1.57	5.4	Ocular and nasal congestion, chest tightness, wheezing	Prednisone Aerolate®
4 D.W.	3.0	150	150	46	1.97	4.35	Nasal congestion, wheezing	Aerolate®, cromolyn metaprotorenol
5 L.G.	4.5	180	150	27	0.2	0.8	Nasal congestion, flushing, of the face, chest tightness	Prednisone, Aerolate® Sudafed®
6 A.W.	3.3	75	75	31	0	0.8	Conjunctival and nasal congestion, chest tightness	Tedral® Decadron Turbinaire®
7 N.T. 1st	5.8	110	90	30	0.8	2.6	Conjunctival congestion and tearing, chest tightness	Prednisone, Aerolate® colchicine, Dimetapp®
N.T. 2nd	4.4	126	—	0	1.0	2.8	Conjunctival congestion and tearing	Prednisone, Aerolate® colchicine

* Minutes after ingestion of aspirin; † B, before challenge level; ‡ A, after challenge maximum level.

§ Regular medications consumed during 24 hr preceding challenges.

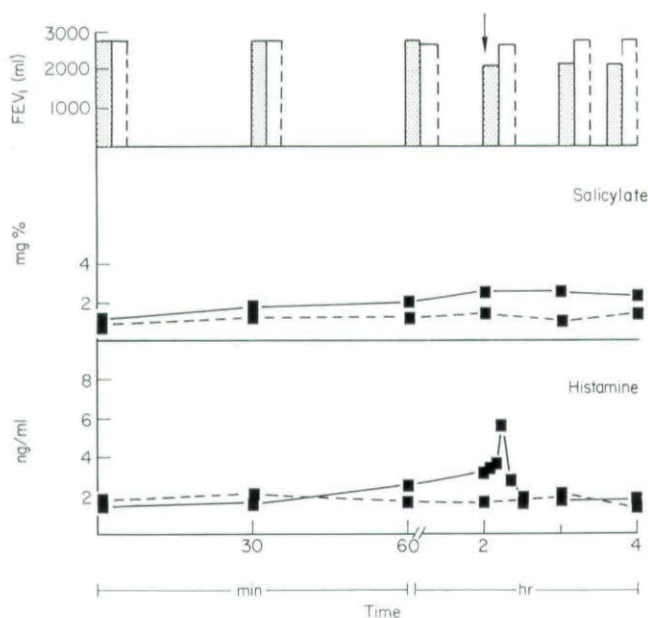


Fig. 1. Patient J.H. During ASA challenge (■—■), there was a late reaction at 2 hr (arrow), with a 26% decline in FEV₁, a slight increase in serum salicylate level and release of histamine into the venous plasma which returned to the baseline level with 30 min. During the Maalox® challenge (■---■), there was no respiratory reaction nor fluctuation in the serum salicylate level or plasma histamine values. Blood samples obtained at 8 and 24 hr were the same as the 4 hr values shown in this figure.

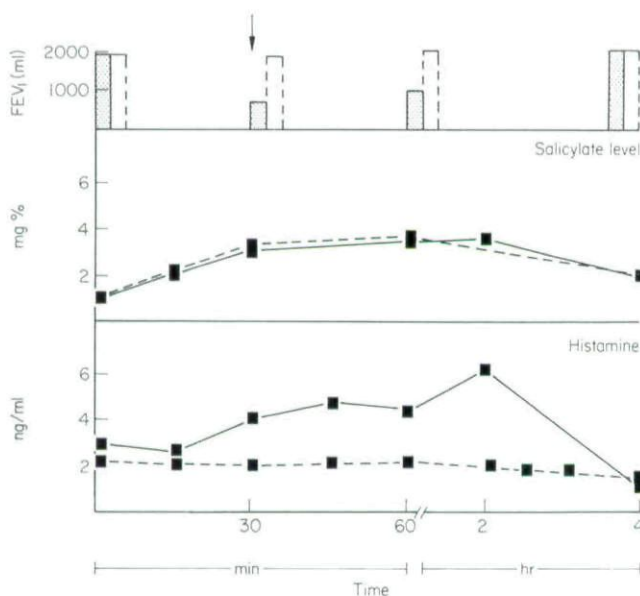


Fig. 2. Patient N.F. There was a fall in FEV₁ at 30 min after ingestion of ASA (■—■). The arrow indicates onset of respiratory reaction. Plasma salicylate levels increased as histamine levels rose. As salicylate levels fell, histamine returned to baseline values, as does the FEV₁. With the sodium salicylate challenge (■---■) there was a rise in plasma salicylates, but no changes in FEV₁ or plasma histamine.

severe reaction occurred much sooner after ingesting ASA, and was associated with an earlier rise in serum salicylate and a simultaneous rise in plasma histamine to 4 ng/ml. In addition, her plasma histamine concentration continued to rise over the next 90 min and did not begin to fall until her respiratory reaction subsided. In Fig. 2, her sodium salicylate challenge is also depicted. In essence, there was no reaction to sodium salicylate, despite its appearance in the serum and as previously described for Maalox® challenge (depicted in Fig. 1 and not shown in Fig. 2) there was no significant change in the baseline plasma histamine concentration of approximately 2 ng/ml.

When the ten non-asthmatic individuals were challenged with either acetyl or sodium salicylate there was the expected rise in serum salicylate levels but no asthmatic reactions and no changes in plasma histamine values. A representative example of this chronological sequence is presented in Fig. 3, where B.S. ingested both acetyl and sodium salicylate and T.N. ingested only ASA. The differences in FEV₁ values are a reflection of their relative heights. It should be noted that unlike asthmatic individuals, venous plasma from non-asthmatic individuals consistently contained low plasma histamine levels (<0.25 mg/ml).

In Fig. 4, the chronological sequence of events which occurred for two ASA 'tolerant' asthmatics (M.S. and M.W.) are presented. These patients behaved quite differently from the other eight control asthmatics. After ingesting ASA they experienced no respiratory symptoms nor changes in FEV₁ values. Their serum salicylate levels rose at 30 and 60 min respectively. However, the most striking finding was a biphasic rise in their plasma histamine, occurring at 30 min and again at 2 hr. These findings are in marked contrast to the remaining eight asthmatic control patients. It is possible that 'control' asthmatics M.S. and M.W. were unsuspected aspirin

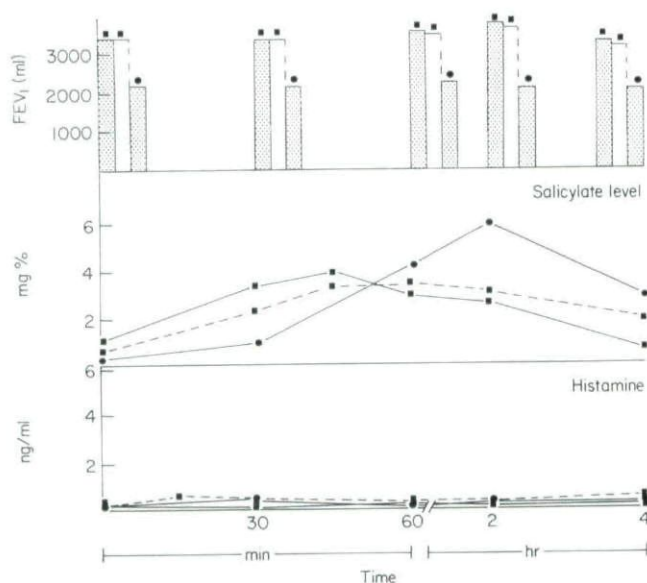


Fig. 3. Two representative non-asthmatic controls, B.S. (■—■) ASA challenge and (■—■) sodium salicylate challenge were both associated with no changes in FEV₁ values and a prompt rise in serum salicylates. T.N. (●—●) ASA challenge produced no change in FEV₁ values, and a marked increase of serum salicylate at 2 hr. Plasma histamine was less than 0.25 ng/ml both before and during all challenges.

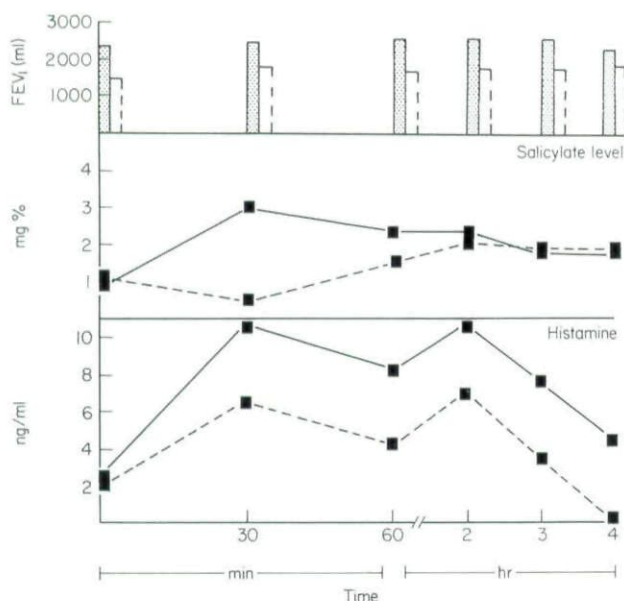


Fig. 4. Two of eight ASA-tolerant patients, patient M.S. (■—■) and M.W. (■---■) underwent control challenges with ASA. There were no respiratory reactions nor changes in FEV₁ values. Their serum salicylate levels rose at 30 and 60 min. However, histamine levels from both patients were found to be strikingly elevated throughout the 4-hr test period, with a peak of histamine at 30 min and again at 2 hr.

intolerant individuals. Both patients are female, between 50 and 60 years of age, with severe asthma and unexplained vasomotor rhinitis. M.S. has had multiple nasal polypectomies and bilateral Caldwell-Luc procedures. These patients were selected for asthmatic controls because they gave a history of tolerating ASA in the past. They were taking dosages of prednisone in the range of 20 mg/24 hr, as well as other standard bronchodilators. Without such medications their lung function would have been too low to conduct oral ASA challenges. Therefore, it is possible that the same medications which prevented natural bronchospasm also protected their bronchial smooth muscles from histamine.

In Table 2, the ASA intolerant asthmatic group is compared to the ASA-tolerant asthmatic group and to the non-asthmatic group. In the sera of the ten aspirin-tolerant asthmatic patients, maximum salicylate levels ranged from 1.6 to 6.2 (mean 3.3) mg% and were observed between 30 and 240 min after aspirin ingestion (mean 114). All remained free of symptoms or changes in FEV₁ values during ASA challenges. The sera from ten non-asthmatic control individuals were found to contain maximum salicylate levels, ranging from 3.5 to 12.8 (mean 6.8) mg% between 45 and 240 (mean 82.5) min after aspirin ingestion. None developed bronchial, ocular or nasal signs or symptoms during the challenges. It can be observed that the ASA-intolerant group falls between the other two groups with respect to maximum salicylate levels and the time of appearance of these values. In Table 2 the mean changes in plasma histamine for aspirin-intolerant and tolerant asthmatics and non-asthmatics controls are recorded. Mean plasma histamine levels before ASA challenges were significantly different when comparing the asthmatic groups to the non-asthmatic controls (1.25 *v.*

Table 2. A comparison of mean salicylate levels and plasma histamine values in asthmatics and control subjects undergoing oral aspirin challenges

Groups	Maximum* salicylate levels (mg%) mean (range)	Time of appearance maximum salicylate levels (min) mean (range)	Mean changes in plasma histamine (ng/ml)	
			Before (B)	After (A)
ASA intolerant asthmatics (7)	4.14 (2.5-6.0)	102.8 (31-180)	1.25	3.74
ASA tolerant asthmatics (10)	3.3 (1.6-6.2)	114 (30-240)	1.25	2.75
ASA tolerant asthmatics (8) (minus M.S. & M.W.)	—	—	1.25	1.25
			$P < 0.001$	$P < 0.001$
Non-asthmatic controls (10)	6.8 (3.5-12.8)	82.5 (45-240)	0.01	0.128

* Maximum levels after ingesting ASA 325 mg. B, before challenge with ASA; A, maximum level after challenge.

Chi-square: no significant differences between three groups with respect to maximum salicylate levels or their time of appearance after aspirin challenges. Differences in mean plasma histamine values were not significant except those P values which are recorded between means.

† Without patients M.S. and M.W., mean was 1.25 ng/ml and difference from mean histamine level in ASA intolerant group was significant ($P < 0.001$).

0.01 ng/ml). Mean plasma histamine level after ASA challenge was 3.74 ng/ml for the aspirin intolerant asthmatics as contrasted to 0.125 ng/ml for the non-asthmatic controls. The mean plasma histamine level in the asthmatic control group was influenced by the two of ten patients whose plasma histamine levels were found to be elevated during the ASA challenges. Therefore this group was not significantly different from the aspirin-intolerant group. However, for the remaining eight control asthmatics, the pre-challenge plasma histamine levels were 1.25 ng/ml, did not fluctuate during their aspirin challenges, and were significantly different from the ASA intolerant group (3.74 *v.* 1.25 ng/ml, $P < 0.001$).

Cell counts

The maximum increase in peripheral basophils and eosinophils after aspirin challenge in aspirin-intolerant asthmatics ranged from 13 to 100% and 11 to 80% respectively. Overall, the basophils rose from a mean baseline value of $38 \pm 11 \text{ mm}^3$ to $58 \pm 32 \text{ mm}^3$. Eosinophils increased from a mean of $233 \pm 269 \text{ mm}^3$ to $302 \pm 351 \text{ mm}^3$. However, none of these changes were statistically significant. The cell counts were unaltered after sodium salicylate challenges in two aspirin-intolerant asthmatics and one non-asthmatic control subject. Cell counts were unchanged during aspirin challenges in tolerant asthmatics. When M.S. and M.W. were separated from the remaining eight, there were still no significant differences observed.

Discussion

In this study we have shown that histamine was increased in the venous plasma of seven aspirin-intolerant asthmatic patients during aspirin-induced asthmatic reactions.

Rising plasma histamine concentrations were measured at the time of increasing plasma salicylate levels and the onset of typical asthmatic reactions in these patients. In addition, the most severe asthmatic responses occurred in those patients where the shortest time elapsed between ASA ingestion and the onset of respiratory reactions and were associated with the highest levels of plasma histamine (L.W. and N.F. in Table 1 and Fig. 2). Furthermore, elevation of plasma histamine occurred only during acetyl salicylate challenges. Two patients (N.F. and A.W.) who developed bronchospasm with simultaneous elevations of histamine in their plasma after ingesting acetyl salicylate, showed no changes in plasma histamine nor did they experience asthmatic reactions after ingesting an identical dosage of sodium salicylate.

In an earlier study, we showed that histamine was released into the plasma of patients with reagin-mediated asthma undergoing specific allergen inhalation challenges (Bhat *et al.*, 1975). Asthmatic episodes which are induced by the ingestion of ASA are also associated with release of histamine into the plasma. Such a finding adds considerable support to the theory advanced by Schlumberger *et al.* (1974) who postulated that histamine is released from the lungs by ASA through a non-immunological pathway and is an important mediator of bronchospasm in the aspirin-induced respiratory reaction.

The appearance of histamine in venous plasma during ASA challenges could result from either the release of histamine from the lungs with transient peripheral circulation or ASA interaction with peripheral blood basophils and release of histamine into the peripheral vascular space. We attempted to clarify this question by the following *in vitro* experiments. Using peripheral leucocytes from either non-asthmatics or aspirin-intolerant asthmatics and adding acetyl salicylate ASA-rich plasma or increasing concentrations of salicylate solutions, we were not able to demonstrate histamine release *in vitro*. In our tests of patient N.F., who showed a significant increase of histamine in her venous plasma during aspirin challenges *in vivo*, no histamine was released from her peripheral leucocytes *in vitro*, after adding either salicylate-rich plasma from normal individuals, her own salicylate-rich plasma, or salicylate solutions. Such *in vitro* studies continue to support the hypothesis that aspirin-induced reactions are not antigen-reagin-mediated immediate hypersensitivity reactions, since release of histamine from peripheral basophils *in vitro* is a classic feature of the latter type of reactions (Lichtenstein & Osler, 1964). A possible interpretation is that the active acetyl radical of aspirin attaches to mast cell membrane receptors, which are found only in aspirin-intolerant asthmatic individuals. This interaction between ASA and the hypothetical receptor then initiates the release of histamine into peribronchial tissues, with spill over into the pulmonary venous circulation, heart, peripheral arterial system and eventually the peripheral venous plasma.

Although our current *in vivo* studies do not provide definitive answers as to the source of plasma histamine which was released during these challenges, there are some studies which support the premise that histamine released in the lungs circulates transiently in the peripheral circulation.

Patterson, Miller & Harris (1975) have recently shown that histamine and SRS-A are released from bronchial basophils and mast cells in Rhesus monkeys undergoing specific antigen challenges. Chiesa *et al.* (1975) induced asthmatic reactions in dogs with antigen challenges and simultaneously sampled peribronchial veins, arterial and venous blood. They showed that venous histamine concentrations rose during antigen challenges, were parallel to histamine levels in arterial samples but always contained

four- to five-fold less histamine than was detected in arterial samples. Prior studies have shown that radio-labelled histamine, injected intravenously, disappears from the circulation in approximately 3 min (Beall & Van Arsdell, 1960). Histamine concentration decreases as it circulates from its point of release, which probably accounts for the relatively low levels of histamine which we detected in venous plasma during our ASA challenges.

A more difficult question is whether or not the histamine which is released during aspirin-induced respiratory reactions contributes to the pathological events in such reactions. Histamine has been studied extensively and its role in producing vasodilation (flushing, peripheral vascular collapse) (Schild, 1956), direct bronchial smooth muscle constriction (Austen, 1971), or activation of bronchial mucosal afferent receptors with reflex cholinergic discharge (Gold, Kessler & Yu, 1972) has been established. Inhalation of histamine in very low concentrations, in the order of 0.03–10 mg/ml of histamine base produces bronchoconstriction in most asthmatic individuals regardless of their clinical asthmatic mechanisms (Spector & Farr, 1975). Furthermore, it has been known for some time that non-asthmatic individuals can inhale substantial dosages of histamine without bronchoconstriction and can be clearly separated from the asthmatic population on the basis of this unresponsiveness (Itkin, 1967).

Many of the clinical characteristics of a severe aspirin-intolerant reaction, such as flushing, peripheral vascular collapse, intense rhinorrhea and bronchospasm are all consistent with histamine-mediated anaphylactic reactions. For purposes of patient safety, we selected aspirin-intolerant asthmatics who had experienced only mild to moderate reactions to aspirin in the past. It is logical to assume that more catastrophic aspirin-induced reactions might be associated with higher levels of plasma histamine if this mediator plays a dominant role in the ASA-induced reaction. In our current series, higher levels of circulating plasma histamine were detected in the two patients (L.W. and N.F., Table 1) who had the most severe reactions.

Although we are inclined to believe that release of histamine and its action on bronchial, nasal and vascular receptors is an important mechanism in ASA-induced asthmatic reactions, additional mediators, such as SRS-A (Orange, Austen & Austen, 1971) and prostaglandins (Sweatman & Collier, 1968), may play important pathophysiological roles, in either early or late asthmatic responses (Pepys, 1973).

Green, Hedgnist & Svanborg (1974) have detected increased plasma levels of prostaglandin $F_{2\alpha}$ after allergen provoked asthma in humans, and recently Nemoto *et al.* (1976) have demonstrated elevated levels of serum prostaglandins in asthmatic patients when compared to normal control subjects. Since aspirin and indomethacin inhibit the formation of prostaglandins *in vitro*, whereas sodium salicylate is non-inhibitory (Vane, 1972) the possibility exists that prostaglandin synthesis *in vivo* is disproportionately altered by ASA with a resulting imbalance in homeostatic control of bronchial patency. In addition, since both prostaglandins (Tauber *et al.*, 1973) and bradykinin (Stoner, Manganiella & Vaughn, 1973) have a profound effect upon the level of cyclic nucleotides in lung tissues, they may modulate primary mediator release or action.

In conclusion, we have presented evidence supporting the hypothesis that histamine is released into the plasma at the onset of the aspirin-induced asthmatic reaction. In some patients, prolonged circulation of histamine was associated with prolonged bronchospasm which diminished as histamine levels returned to normal. The aspirin-

induced bronchospastic events are probably more complex than the above statement suggests. Clearly, further studies will be required in order to identify additional mediators or mechanisms.

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