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Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma

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Summary

One-hundred and forty asthmatics were tested perorally with acetylsalicylic acid (ASA), and/or with the azo-colour tartrazine; a fall in PEF of more than 20% was accepted as a positive result. About one quarter of the patients displayed a positive reaction to one of the two tested agents. No significant correlation was found between the reactions of these, and the presence of atopy, nasal polyposis, sinusitis, rhinitis, sensitivity to cold air, the age at onset, duration of asthma, or history of sensitivity to alcoholic drinks. The history suggested sensitivity to ingested, possibly coloured, food and drink, in only about one third of the tartrazine-positive cases. The ASA provocation tests were mainly applied to patients with doubtful or negative histories of sensitivity to ASA-containing drugs. The frequency of cross-reactivity between the two tested agents was statistically significant; patients reacting to tartrazine were for the most part, also sensitive to ASA. Tests for sensitivity to analgesics and food additives should be conducted as a routine measure in asthmatics, and sensitive patients should be given information on suitable medication and dietary control.

Introduction

Reports have indicated that symptoms of hypersensitivity to acetylsalicylic acid (ASA) in asthmatics mainly develop after middle age, and are found predominantly in non-atopic patients. In ASA-sensitive patients, it is stated that nasal symptoms and signs such as polyposis, perennial rhinitis or swelling of the mucosa of the nasal sinuses are frequent. These symptoms often precede the manifestation of asthma by months or years (Samter & Beers, 1967, 1968; Giraldo, Blumenthal & Spink, 1969). The intake of ASA may not only exacerbate the asthma, but also induce collapse, anaphylaxia, rhinitis, angioedema, headache, urticaria and gastrointestinal colic (Samter & Beers, 1967, 1968). Many reports (Samter & Beers, 1968; Chafee & Settipane, 1974; Settipane, Chafee & Klein, 1974) state that atopy is to be found in about 10% or less of patients sensitive to ASA. Reactions similar to those with ASA may also be induced by indo-

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methacin (Samter & Beers, 1967), mefenamic acid, pyrazolone, dextropropoxyphene, metamizole, phenylbutazone and paracetamol (Smith, 1971), or by food additives such as azo-colours or benzoic acid (Juhlin, Michaëlsson & Zetterström, 1972). Patients sensitive to an analgesic are frequently often sensitive to an azo-colour and/or benzoic acid (Samter & Beers, 1968; Smith, 1971; Rosenhall & Zetterström, 1973).

Although hypersensitivity reactions to ASA or to food additives may be diagnosed by peroral testing there are considerable variations in the methods of administering the tested agents, the initial dose, and the criteria for assessment of the results (McDonald, Mathison & Stevenson, 1972; Lockey, 1973; Rosenhall & Zetterström, 1973).

The pathogenesis of ASA hypersensitivity is unknown. Little evidence is available of any immunological mechanisms that may be involved (Giraldo *et al.*, 1969; Yurchak, Wicher & Arbesman, 1970), although work by De Weck (1971) and Phills, Perelmutter & Liakopoulou (1972) has suggested that in certain cases antibodies to ASA or conjugates may be detectable. *In vitro* studies on the mechanism of action of aspirin-like drugs seems to confirm their ability to block anaphylaxis, through the inhibition of prostaglandin synthesis and/or release (Vane, 1971; Higgins & Braunwald, 1971; Piper & Walker, 1973). In some asthmatics, an abnormal mechanism may exist causing ASA to block only those prostaglandins with a bronchodilating effect (PGE_2), but not to block the release of $PGF_2\alpha$, which is a bronchoconstrictor (Settipane *et al.*, 1974).

The present investigation was undertaken with a view to better understanding of the frequency, distribution and clinical picture of hypersensitivity reactions to ASA and tartrazine in our own patients. Our endeavours were not confined to discovery of those cases with severe and clinically obvious reactions, but also of those in whom only moderate bronchial obstruction was elicited on testing. It was hoped that the results would help decide whether tests for ASA and azo-colour hypersensitivity should be included in our clinical routine.

Material

Patients

The series comprised 140 female patients, who were examined for hypersensitivity reactions to acetylsalicylic acid (ASA) and tartrazine, by means of history-taking and peroral provocation tests (Table 1). A patient was called 'atopic' if she had two or more positive reactions on skin-testing with a batch of common allergens, or one positive skin test which was either confirmed by bronchial challenge, or in combination with a history of flexural eczema. Patients with no evidence of immediate sensitivity on skin-testing were termed 'non-atopics'. A third group, classified as 'undefined', consisted of patients to whom the criteria mentioned were inapplicable. Inhalation provocation tests with common allergens were made only if they were regarded as necessary for the general care or treatment of the patient.

No statistical differences were present between the groups in respect of age, the age at onset of the symptoms, or their duration. In only four patients, however, all of them in the atopic eczema group, was there a history of onset of the asthmatic symptoms before the age of 15.

All of the patients had clinically obvious asthma which fulfilled the criteria set by the Ciba Guest Symposium (1959), and were admitted to hospital either for examina-

Table 1. Characteristics of the patients

	'Atopics'	'Non-atopics'	'Undefined'
No. of cases	50	75	15
Age (years) mean	39·8	49·4	45·8
Age (years) range	18–67	18–78	20–79
Age of onset (years) mean	31·3	38·6	30·8
Age on onset (years) range	2–56	5–79	2–51
Duration of symptoms (years) means	7·2	10·5	16·5
Duration of symptoms (years) range	1–42	1–50	1–49
Positive bronchial challenge test with common allergen			
No. of cases	26	—	—
% of cases	50		
History of atopic eczema			
No. of cases	21	—	5
% of cases	42		33
History of nasal polyps			
No. of cases	5	18	1
% of cases	10	24	0·5
History of rhinitis			
No. of cases	34	59	6
% of cases	68	78	40
Sinusitis (mucosal swelling) on X-ray			
No. of cases	21	54	11
% of cases	42	72	73

tion, or by reason of exacerbation of the disease. Most patients has sputum and/or blood eosinophilia, and the majority of them had never smoked.

Methods

The details of history were obtained with a questionnaire designed for the present study. Information was sought on known or suspected sensitivity to analgesics, reactions to ingested food and drink, the prevalence of atopic eczema, rhinitis or nasal polyps, and the age at onset of the asthma. An X-ray picture of the nasal sinuses was taken in all patients. In those cases with a definite history of ASA sensitivity, tests were made with tartrazine alone. For practical reasons, the patients in only one (female) ward were included in the study, the tests being conducted whenever practicable, and regardless of the nature of the patients' asthma, or the expected results of the test.

Forty-eight hours before the challenge tests, a patient was put on a diet advised by the hospital dietician. As far as possible, this diet was free from added or natural salicylates, benzoates or artificial food colouring, so as to avoid uncontrolled ingestion of the tested agents, or chemicals related to them.

Antihistamine drugs were omitted for 48 hr, and bronchodilator treatment for 6 hr prior to the tests. Daily doses of 10 mg prednisolone or less were maintained. The test method applied was a slight modification of that described by Rosenhall & Zetterström (1973). At 9 a.m. a patient received one capsule of placebo, on an empty stomach; this was followed by identical capsules, supplied by Oy Orion Ab, containing 0·1, 1,

10 or 100 mg of ASA, or 0·1, 1, or 10 mg of tartrazine, given every 40 min. Peak expiratory flow (PEF) was measured with a Wright Peak Flow Meter at the end of each 40-min period, with the highest reading from three consecutive blows being noted, until the test was positive or the maximal dose was reached. The baseline PEF was 200 l/min or more in all patients, with a mean value of 327 l/min. The provocation test was regarded as positive if the fall in PEF was 20% or more, and doubtful if the fall was 15–20%. Records were kept of other reactions such as headache, malaise and skin eruptions. In all, 245 tests were made. Twenty-six patients were tested with ASA only, eighteen with tartrazine only, and ninety-six patients with both agents.

Results

Bronchial obstruction

A positive ASA provocation test was observed in about one quarter of the cases; the positive cases were evenly distributed in the atopic, nonatopic, and undefined groups (Fig. 1). Tartrazine reactions occurred somewhat more frequently in the non-atopic group, although the difference is not statistically significant. Slightly more than one fifth of the tartrazine provocation tests gave positive results (Fig. 1). The mean fall in PEF after ASA challenge in the positive cases amounted to 37·7% (range = 20–74%), and after tartrazine to 38·1% (range = 20–59%). A fall of more than 30% was

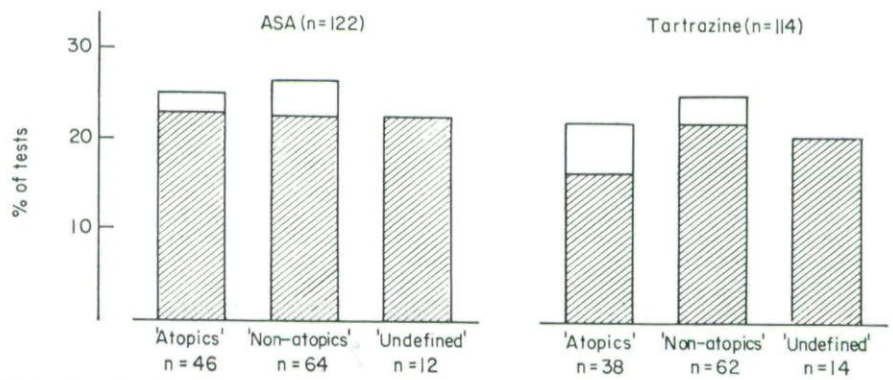

Fig. 1. Results of provocation tests with ASA and tartrazine. ▨, Positive results; □, doubtful results.

noted with ASA in nineteen cases, and with tartrazine in seventeen cases; these amount to 61% and 68% respectively of the positive tests. A few severe reactions, combined with a reduction in PEF of 50% or more and marked dyspnoea, occurred in five cases with ASA, and in seven cases with tartrazine.

Other reactions

Reactions other than asthmatic ones were recorded in seventeen cases (Table 2). In one case, urticaria was provoked by both ASA and tartrazine, and was combined with slight laryngeal oedema (case No. 2). In five cases, either or both of the test drugs induced general itching of the skin; in case No. 16, this was accompanied by general skin erythema. Other reactions were malaise (four cases), headache (two cases), rhinitis, blocked nose or itching of the nose in three cases, dizziness in one case, and facial oedema in two cases. Table 2 shows that these reactions were not always combined with bronchial obstruction.

Table 2. Reactions other than asthma after peroral provocation test with ASA and tartrazine (seventeen patients)

	ASA		Tartrazine	
Case no.	Symptoms and signs	Results of provocation test	Symptoms and signs	Results of provocation test
1	Not done		Head 'heaviness'	+
2	Urticaria, hoarseness	−	Urticaria, hoarseness	−
3	Itching, blocked nose	−	Blocked nose	Doubtful
4	Rhinitis, oppression	+	Rhinitis, blocked nose	+ (after 12 hr)
5	Itching, malaise	+	Not done	
6	Sweating, malaise	−	Not done	
7	Fatigue	−		−
8	Facial oedema	+		+
9	Malaise	Doubtful		−
10		Doubtful	Itching	+
11		−	Headache	Doubtful
12	Dizziness	+		−
13	Not done		Malaise, facial oedema	−
14	Itching of nose	−	Not done	
15	Itching	−		−
16	Itching, erythema of skin	+		−
17	Malaise, headache	+		Doubtful

Table 3. Comparison of reactions to ASA with those to tartrazine in patients tested with both agents (ninety-six patients)

	Tartrazine tests			
ASA tests	Positive	Doubtful	Negative	Total
Positive	11	4	10	25
Doubtful	2	1	3	6
Negative	4	2	59	65
Total	17	7	72	96

$\chi^2 = 27{\cdot}1$.
$P < 0{\cdot}001$.

Reactions to both ASA and tartrazine

In the ninety-six patients challenged with both ASA and tartrazine, about one half of the positive ASA cases also had a positive tartrazine test. About three fifths of the tartrazine positive cases also reacted to ASA (Table 3).

Doses eliciting reactions

In one case, urticaria was provoked by no more than 0·1 mg of ASA, and 0·1 mg of tartrazine. In one patient, a fall in PEF of 30% occurred after 0·1 mg of ASA, and in

two there were falls in PEF of 49% and 40% respectively after the 1 mg dose. All of the other reactions took place after the administration of maximal doses, i.e. 100 mg of ASA or 10 mg of tartrazine.

Nasal polyps, rhinitis and sinusitis

In those cases with nasal polyps in whom provocation tests were made, hypersensitivity to tartrazine and/or ASA was found in about one half (Tables 4a and 4b). The majority of the patients with positive provocation tests had a negative history of polyposis. No statistically significant difference was apparent in the prevalence of rhinitis or sinusitis (i.e. swelling of the mucosa, or findings on X-ray of the paranasal sinuses) in the ASA or tartrazine positive groups as compared with the negative-test groups.

Table 4 a and b. History * of nasal polyposis (n.p.) and results of provocation † with ASA and tartrazine

(*a*) *ASA*

	Provocation test		
History of n.p.	Positive	Negative	Total
Positive	7	21	28
Negative	13	61	74
Total	20	82	102

(*b*) *Tartrazine*

	Provocation test		
History of n.p.	Positive	Negative	Total
Positive	5	20	25
Negative	11	59	70
Total	16	79	95

* Cases with unavailable or doubtful history not included.
† Cases with doubtful provocation tests not included.

Hypersensitivity to cold air, age at onset, and duration of asthma

Cold air provoked asthma in 71% of the ASA positive cases, and in 80% of the tartrazine positive cases. However, hyper-reactivity of this type was present as frequently in cases with negative provocation tests.

In terms of age at onset or duration of symptoms, no statistically significant difference was apparent between those giving positive or negative tests to ASA or tartrazine.

Correlation between tests and history

Eleven out of thirty-one ASA-positive cases (35%) suspected that they were hypersensitive to ASA. Of three cases with positive histories of reactions to analgesics other

Table 5. Tartrazine sensitivity and history of reactions to food or drink possibly containing azo-colours (114 patients)

	Tartrazine provocation test			
History	Positive	Doubtful	Negative	Total
Positive	9	4	7	20
Negative	16	4	70	90
Uncertain			4	4
Total	25	8	81	114

than ASA, one had a positive, one a doubtful, and one a negative ASA test. Eight patients reported asthma following the ingestion of berries or fruit. Of these, six were ASA-sensitive. Nine patients out of twenty-five tartrazine-positive cases (36%) gave a history of aggravation of the asthmatic symptoms after the ingestion of either coloured tablets (analgesics excluded), certain foods such as flavoured yoghourt or packet soups, or various types of commercial fruit juice or carbonated drinks. Seven additional patients gave such histories which were not confirmed in the tartrazine test (Table 5). Sixteen cases reported aggravation of asthma by alcoholic drinks and only five (31%) had positive ASA and/or tartrazine tests.

Discussion

The series under study here is representative of female in-patient asthmatics in the University Central Hospital, with severe cases excluded.

Different methods of testing make it difficult to compare our results with those obtained in other investigations. It can be assumed that the frequency of positive reactions in this series exceeds that in reports in which the presence of ASA or tartrazine sensitivity has been judged purely by the observation of clinically obvious symptoms (Samter & Beers, 1968), or by a fall in PEF of more than 50% (McDonald *et al.*, 1972). Furthermore, the relationships reported here between positive reactions and other factors, such as atopy or nasal polyps, may also be influenced by the method adopted in recording, and have to be borne in mind in the evaluation of our findings.

In deciding to regard a fall in PEF of more than 20% as a positive test finding, it was known that spontaneous diurnal changes might influence the results. Recording of the PEF over several days would be necessary to establish the natural variability of each patient, and repeated provocation tests would add to the reliability of the results. Many researchers have demonstrated that the diurnal variations in asthmatics normally include a tendency towards spontaneous bronchodilatation through the late morning hours, with a peak at noon. In a few cases, however, the opposite may be the case (Israels, 1951; Lewinsohn, Capel & Smart, 1960; Scherrer & Aepli, 1964; Muittari, 1969). For the time being, however, it seems that the reactions to ASA and tartrazine reported here should be regarded as hypersensitivity to the tested agent.

Fisherman & Cohen (1973, 1974) have suggested that the Sequential Vascular Response Test could be employed for the detection of ASA sensitivity. The test shows close correlation with clinical symptoms and signs. In this test, it seems possible to administer only very low doses of ASA to the patient, which makes the testing procedure safer.

The terms 'atopic' and 'atopy' have no exact meaning in everyday medical language, and they need to be defined whenever they are employed in scientific text. In this report these terms have been used to distinguish a group of patients with signs of immediate sensitivity to common allergens, the main feature of atopy (Pepys, 1975). Samter & Beers (1968) who have defined the 'atopic' group in slightly different terms, found more ASA sensitivity in the non-atopic than in the atopic group. These findings were confirmed by Chafee & Settipane (1974), their criteria for atopy being the presence of positive skin tests. Their series included children. Giraldo *et al.* (1969) found positive skin tests in approximately 50% of their ASA-sensitive patients. In this study, no difference was found in the reactions to ASA and tartrazine in our 'atopics', as compared with the non-atopic patients. Although the results of prick-testing seem to bear a close correlation with serum IgE (Stenius *et al.*, 1971), their relevance to the symptoms of the patients termed 'atopics' in this study is not clear. For various reasons, not all patients were subjected to inhalation provocation tests with common allergens. As was recognized by Samter & Beers in 1968, many asthmatics, who early in life exhibit marked atopic sensitivity, may later change, so that the clinical picture resembles cryptogenic asthma, with perennial symptoms, and more severe disease. Many of our asthmatics came within this group. Other patients may have atopic eczema and hay fever, but later in life develop asthma, which is clinically of the cryptogenic type. In these groups, the skin sensitivity seems to persist.

In the series described by Giraldo *et al.* in 1969, all of the reactions to aspirin occurred within 2 hr. The bronchial obstruction reported in the present series took place within 40 min. It is probable that any subsequent asthmatic reactions were obscured by routine bronchodilating medication, which was administered to most patients after the test. The testing procedures did not cause any serious complications.

It may be that the test doses of ASA given here were too low for the detection of all sensitive cases. The ASA-dose in an ordinary tablet for pain relief is normally about 500 mg. It is intended in future to raise the test dose to this level. As concerns tartrazine, a bottle of orangeade contains about 2–8 mg; in our opinion, a maximal test dose of 10 mg of tartrazine is adequate.

In confirmation of the observations made by Rosenhall & Zetterström (1973), and Samter & Beers (1968), two of the present patients with positive ASA-tests stated that they could take aspirin without trouble, and that on occasion they even used it as a remedy for their asthma. In some patients, it is possible that the effects of ASA are selective and dose-dependent. Small doses of ASA may inhibit only the bronchodilating prostaglandins, inducing bronchial obstruction in the patient, whereas large doses may inhibit all prostaglandins, with either no effect upon the bronchi or bronchodilatation (Zetterström, 1972).

Samter & Beers (1967) found intolerance to indomethacin in all of their eighteen cases of ASA sensitivity. They further reported that in the ASA-sensitive group other minor analgesics, such as dextropropoxphene and phenylbutazone, or azo-colours, frequently induced symptoms in ASA-sensitive patients. In the present investigation, consistent results (either both tests positive, or both negative) of the ASA and tartrazine tests were found in 83% of cases. It is considered necessary that all patients with sensitivity to either agent should be advised to avoid both analgesics and azo-colours, as discussed below.

Chafee & Settipane (1974) found that urticaria was more frequent in ASA-sensitive patients with rhinitis alone, than in patients with asthma. In the current series, only

one was found to react with urticaria when tested with ASA and tartrazine; in this patient, these agents did not induce asthma.

It has been shown that nasal polyposis is present in about 50% of patients with ASA hypersensitivity (Samter & Beers, 1968; Giraldo *et al.*, 1969). Delaney (1975), in a series of fifty patients with ASA hypersensitivity, reported nasal polyps in forty-eight of these cases. However, in a series of 100 patients with nasal polyps, only three displayed ASA hypersensitivity. In this investigation, the presence or absence of polyposis was evaluated by means of history alone. This fact, in addition to those mentioned above in regard to the method applied for evaluation of test results, may explain why it was found impossible to confirm previous findings that nasal polyposis is a typical feature in ASA-sensitive patients.

Hyper-reactivity of the bronchial tree to non-specific stimuli, such as cold air, is typical in asthmatics; Samter & Beers (1968) have reported sensitivity to change of weather or to other sensory stimuli in 60% of ASA-sensitive cases. In the present series, hyper-reactivity to cold air was common, but unrelated to ASA sensitivity. It is evident that the mechanisms of these two causes of bronchial obstruction differ from one another. Simonsson, Jacobs & Nadel (1967) showed that cold air stimulates the cough reflex in the upper airways, which in turn may lead to bronchospasm.

Giraldo *et al.* (1969) reported a higher age of onset of asthma in the ASA-sensitive group, as compared with his whole series. This could not be confirmed, probably because of the different composition of our series.

In this series, only 35·5% of the patients positive to ASA gave a history that suggested sensitivity to analgesics, although they could not name the agent which actually caused their symptoms. For fear of violent reactions ASA tests were not made in patients with a definite history of ASA sensitivity.

Juhlin & Michaëlsson (1973) have stated that 100 g lingon berries (*Vaccinium vitis-idaéa*) contain 2–6 mg salicylic acid, and 20–100 mg benzoic acid, and that small amounts are present in many other fruits and berries. This may explain the asthmatic symptoms induced by the ingestion of fruits and berries reported by some of our ASA-sensitive patients. Juhlin & Michaëlsson (1973) suggested that wines and beers may contain agents causing similar reactions to salicylates and benzoates, but in the present instance no connection was apparent between ASA and tartrazine sensitivity, and a history of sensitivity to alcoholic drinks.

Forty-eight per cent of the tartrazine-sensitive patients gave histories of reactions to food and drink that possibly contained colouring matter. For the most part, the patients thought that the symptoms were induced by the main ingredients. To judge from the many comparatively slight reactions to tartrazine recorded in this series, it may be that some patients never have a frank attack of asthma after the ingestion of azo-colours or preservatives. Nonetheless, they may have moderate but constant bronchial obstruction, only partly controlled by medication. Without exact knowledge of the existence and occurrence of food additives, and of natural salicylates and benzoates, the patient finds it difficult to relate symptoms to any ingested food or drink. In our opinion, all adult asthmatics should be tested as a routine measure with at least ASA and one azo-dye. More investigations are needed for clarification of whether other related agents, benzoates in particular, should also be included in the routine.

All of the patients in our care, with known or suspected sensitivity to any analgesics or food additives, have been given uniform advice. They have been told to avoid ASA,

dextropropoxyphene, metamizole, butazolidine and indomethacin, and have been given a list of all the preparations on the market that contain these agents. It is possible that the list should be extended also to contain pentazocine, mephenesic acid and phenazones. The only reactions observed by us have been to the first mentioned of these. Although sensitivity reactions to paracetamol have been reported (Smith, 1971), no such reactions have been observed in our clinic. In pursuance of the practice adopted by Rosenhall & Zetterström (1973), ASA-sensitive patients have been advised to use paracetamol as an analgesic. If spasmolytic or anticholinergic treatment is needed, we use atropine or glycopyrronum bromide in order to avoid metamizole which in our country is a component of some spasmolytic preparations.

Lockey (1973) and Rosenhall & Zetterström (1973) have published detailed lists of goods which may contain certified food additives, but legislation and practice vary from country to country. Publications on the occurrence of natural salicylates and benzoates are also available (Lockey, 1971; Juhlin & Michaëlsson, 1973). Partly on the basis of these and partly on information compiled from almost all Finnish manufacturers of food preparations such as packet soups, sausages, yoghourt, biscuits, and so on, we have, with the hospital dietician, prepared diet lists. It is difficult to make these complete, and up to date. The best solution would obviously be to establish an international agreement on compulsory and complete declaration of contents, and a general restriction on the use of azo-dyes. Unfortunately, azo-dyes are also used widely in medicines; twenty-six of the twenty-nine peroral penicillin preparations available in Finland contain azo-dyes. Patients have been asked to avoid coloured drugs, and whenever possible have been given advice in regard to named preparations based on information from all drug manufacturers on the Finnish market.

References

Chafee, F.H. & Settipane, G.A. (1974) Aspirin intolerance. 1. Frequency in an allergic population. *Journal of Allergy and Clinical Immunology*, **53,** 193.

Ciba Foundation Guest Symposium (1959) *Thorax*, **14,** 286.

Delaney, J.C. (1975) Asthma, nasal polyposis, and aspirin idiosyncrasy. In: *Proceedings of the British Society for Allergy and Clinical Immunology. Clinical Allergy*, **5,** 234.

De Weck, A.L. (1971) Immunological effects of aspirin anhydride, a cotanminant of commercial acetylsalicylic acid preparations. *International Archives of Allergy*, **41,** 393.

Fisherman, E.W. & Cohen, G.N. (1973) Aspirin disease, L-histidine and the sequential vascular response test. *Annals of Allergy*, **31,** 555.

Fisherman, E.W. & Cohen, G.N. (1974) Cholinergic and adrenergic stimulation correlated with aspirin intolerance (hypersensitivity). *Annals of Allergy*, **33,** 209.

Giraldo, B., Blumenthal, M.N. & Spink, W.W. (1969) Aspirin intolerance and asthma. *Annals of Internal Medicine*, **3,** 479.

Higgins, C.B. & Braunwald, E. (1972) The prostaglandin: biochemical, physiologic and clinical considerations. *American Journal of Medicine*, **53,** 92.

Israels, A.A. (1951) *Asthma bronchiale, etterige (bacteriële) bronchitis en het endocrine systeem.* Thesis, Groningen.

Juhlin, L., Michaëlsson, G. & Zetterström, O. (1972) Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *Journal of Allergy and Clinical Immunology*, **50,** 92.

Juhlin, L. & Michaëlsson, G. (1973) Förbjudet och tillåtet vid överkänslighet för konserveringsmedel och färgämnen. *Läkartidningen*, **70,** 1414.

Lewinsohn, H.C., Capel, L.H. & Smart, J. (1960) Changes in forced expiratory volumes throughout the day. *British Medical Journal*, **1,** 462.

Lockey, S.D. (1971) Reactions to hidden agents in foods, beverages and drugs. *Annals of Allergy*, **29,** 461.

LOCKEY, S.D. (1973) Drug reactions and sublingual testing with certified food colors. *Annals of Allergy*, **31,** 423.

MCDONALD, J.R., MATHISON, D.A. & STEVENSON, D.D. (1972) Aspirin intolerance in asthma. Detection by oral challenge. *Journal of Allergy and Clinical Immunology*, **50,** 198.

MUITTARI, A. (1969) *Experiments on bronchomotor responses to bronchodilators and to metacholine in asthmatic patients.* Thesis, Helsinki.

PEPYS, J. (1975) *Clinical aspects of immunology*, 3rd Edn. (Ed. by P.G.H. Gell, R.R.A. Coombs and P. J. Lachmann), p. 877. Blackwell Scientific Publications, Oxford.

PHILLS, J.A., PERELMUTTER, L. & LIAKOPOULOU, A. (1972) Employment of the rat mast cell technique to separate immunologic from nonimmunologic types of allergic reactions to aspirin. *Journal of Allergy and Clinical Immunology*, **49,** 97.

PIPER, P.J. & WALKER, J.L. (1973) The release of spasmogenic substances from human chopped lung tissue and its inhibition. *British Journal of Pharmacology*, **47,** 291.

ROSENHALL, L. & ZETTERSTRÖM, O. (1973) Astma utlöst av analgetika, livsmedelsfärg och konserveringsmedel. *Läkartidningen*, **70,** 1417.

SAMTER, M. & BEERS, R.F. (1967) Concerning the nature of intolerance to aspirin. *Journal of Allergy*, **40,** 281.

SAMTER, M. & BEERS, R.F. (1968) Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Annals of Internal Medicine*, **68,** 975.

SCHERRER, M. & AEPLI, R. (1964) Lung function and bronchodilating drugs. In: *Bronchitis II, an International Symposium* (Ed. by N.G.M. Orie and H.J. Sluiter), p. 273. Royal van Corgum, Netherlands.

SETTIPANE, G.A., CHAFEE, F.H. & KLEIN, D.E. (1974) Aspirin intolerance. II. A prospective study in an atopic and normal population. *Journal of Allergy and Clinical Immunology*, **53,** 200.

SIMONSSON, B.G., JACOBS, F.M. & NADEL, J.A. (1967) Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airways disease. *Journal of Clinical Investigation*, **46,** 1812.

SMITH, A.P. (1971) Response of aspirin-allergic patients to challenge by some analgesics in common use. *British Medical Journal*, **2,** 494.

STENIUS, B., WIDE, L., SEYMOUR, W.M., HOLFORD-STREVENS, V. & PEPYS, J. (1971) Clinical significance of specific IgE to common allergens. I. Relationship of specific IgE against *Dermatophagoides* spp. and grass pollen to skin and nasal tests and history. *Clinical Allergy*, **1,** 37.

VANE, J.R. (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature and New Biology*, **231,** 232.

YURCHAK, A.M., WICHER, K. & ARBESMAN, C.E. (1970) Immunologic studies on aspirin. Clinical studies with aspiryl–protein conjugates. *Journal of Allergy*, **46,** 245.

ZETTERSTRÖM, O. (1972) Astma, atopi och analgetikaintolerans. *Draco pro Medico*, **6,** 1.