

Analgesics, Allergy and Asthma

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Summary

Intolerance to analgesics is common in patients with bronchial asthma, nasal polyps and urticaria. Symptoms of intolerance resemble those of allergy, but the events precipitating them can rarely be traced to reactions between the drug and a specific antibody or sensitised T-lymphocytes. In 8 to 20% of adult asthmatics, aspirin and several other analgesics provoke asthmatic attacks, probably through inhibition of cyclo-oxygenase. This is a distinct and important clinical syndrome with a specific history, course and clinical presentation and a number of unique peculiarities which still require elucidation at the biochemical level.

Up to 40% of patients with chronic urticaria develop an obvious increase in weals and swelling after taking aspirin. These reactions occur only when urticaria is active, and though the reason for them is not known, it appears that different mechanisms may be responsible in different patients. Skin reactions other than exacerbation of chronic urticaria are less common, but may create serious clinical problems.

The clinical background of a patient often determines the type of adverse response to an analgesic. Thus, in certain individuals, analgesics can produce anaphylactic reactions and/or urticaria, probably through an immunological mechanism, while in some asthmatics they precipitate bronchoconstriction, probably through inhibition of bronchial cyclo-oxygenase. Study of untoward reactions to analgesics not only leads to safer pharmacotherapy, but it also offers a fascinating model for better understanding of some diseases.

Most people tolerate aspirin and other anti-inflammatory analgesics well. In some diseases (for example, asthma or urticaria) intolerance to analgesics is frequent and constitutes a major clinical problem. It may present as anaphylactic shock, bronchospasm, angioedema, urticaria or various skin eruptions. These symptoms suggest an allergic background, which indeed is the case in some patients. In others, we are faced with pseudo-allergy.

Ideally, the term allergy or hypersensitivity should be restricted to those reactions in which an

immunological mechanism is present or, at least, presumed. Such a mechanism is often difficult to establish with certainty. Pseudo-allergic reactions have similar clinical manifestations and may share common pathogenic mechanisms, but the initiating event does not appear to involve a reaction between the drug and specific antibodies or sensitised T-lymphocytes (De Sworte, 1984). This paper describes the clinical manifestations of allergic and pseudo-allergic reactions to analgesics and discusses their basis as well as treatment and preventive measures.

1. Systemic Anaphylaxis

This reaction, characterised by the appearance of a generalised flush, palpitations, weakness, dizziness, tingling of the extremities, urticaria, angioedema and apprehension, appears within a few seconds to a few minutes after administration of a drug. If not treated, it may rapidly progress to respiratory distress, shock, seizures, cyanosis, coma and death. A number of anaphylactic reactions, including shock, were reported following administration of the recently marketed zomepirac and its close congener, tolmetin (Del Favero, 1983). Diclofenac, at an oral dose of 25mg, was also reported to produce shock accompanied by a high fever in an elderly man (Dux et al., 1984). In patients with lupus erythematosus or with aspirin-induced asthma, severe reactions to analgesics may take the form of anaphylactic shock. Shock precipitated by analgesics has become a subject of growing interest (Fein, 1971; Hanks, 1982).

Anaphylactic shock is one of a range of untoward reactions to these drugs which include urticaria, maculopapular rashes, angioedema and bronchospasm (O'Brien and Bagby, 1985). They can all be grouped as allergic or pseudo-allergic (Czerzawska-Mysik and Szczeklik, 1981; Szczeklik et al., 1977a, 1985a). The 2 groups differ distinctly in clinical presentation and in tolerance, according to the different analgesics considered. Their differentiation is of clinical importance and may be facilitated by skin tests.

In our department, 136 patients presenting allergic reactions to pyrazolones were reviewed and classified according to true allergic or pseudo-allergic mechanisms. In true allergic reactions, anaphylactoid reaction is the leading syndrome. Other manifestations include angioedema, urticaria or maculopapular rash. Asthmatic attacks occur in only 8% of this group. In contrast, patients with pseudo-allergic reactions usually present with asthmatic attacks. Hypotension, pallor and other symptoms of shock appear only in sporadic cases, with the most severe asthmatic attacks necessitating intensive care. Patients in the pseudo-allergic group invariably have a history of chronic rhinitis

or asthma, but these diseases are much less common among subjects with truly allergic reactions. Other reviews of aspirin allergy showed similarly both true allergic and pseudo-allergic syndromes (Conti et al., 1984; Girard and Gumowski, 1983; Hubert et al., 1984; Schiavino et al., 1981).

Challenge tests with analgesics reveal further differences. In patients with true allergic reactions to dipyrone and/or aminopyrine (aminophenazone), acute clinical symptoms can be reproduced by oral administration of minute amounts of either drug. Such tests, however, even when performed with great caution, carry a substantial risk of precipitating anaphylactic shock. Skin tests represent a safer approach, but generally are positive in 25% or less of patients with a clear-cut history of anaphylactoid reactions (Antépara et al., 1981; Przybilla et al., 1985; Schiavino et al., 1981). In contrast, all our patients, studied 2 to 12 months after acute allergic reactions, had a usually positive intradermal skin test to 0.01% aqueous solutions of dipyrone, 70% of them responded also to 0.001% dipyrone, and 50% to 0.001% aminopyrine. In all these patients oral challenge tests with therapeutic doses of aspirin, indomethacin, fenoprofen, ibuprofen, mefenamic acid, paracetamol, benzydamine, phenylbutazone and sulphinpyrazone were negative.

On the contrary, patients from the pseudo-allergic group were all intolerant to aspirin, which, at doses of 20 to 100mg, precipitated acute asthmatic attacks, often accompanied by rhinorrhoea and facial flushes. Similar reactions were evoked by indomethacin 5 to 20mg, dipyrone 50 to 500mg and aminopyrine 30 to 150mg (Szczeklik et al., 1985a).

Different mechanisms appear to operate in the 2 groups. In the first, prostanoid involvement can be excluded, since several cyclo-oxygenase inhibitors, including aspirin, are harmless in these patients. A true allergic mechanism seems likely because: (1) aminopyrine and its close chemical congener, dipyrone, both evoke anaphylactic shock and/or urticaria in these patients; (2) skin tests with these drugs are positive; (3) skin tests with phenylbutazone and sulphinpyrazone are negative; and

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(4) patients can take these latter drugs with impunity. Phenylbutazone and sulphinpyrazone are pyrazolidines; their basic structure differs markedly from that of the pyrazolone derivatives aminopyrine and dipyron, and they are not generally used as analgesics.

In the second group, reactions are of the pseudo-allergic variety. Patients in this group suffer from aspirin-induced asthma. Bronchoconstriction and rhinorrhoea are the hallmarks of the adverse reactions, which, in our opinion (Szczeklik and Czerniawska-Mysik, 1976), are caused by inhibition of cyclo-oxygenase.

Anaphylactic shock requires prompt, energetic treatment. Adrenaline is given intramuscularly in a dose of 0.5-1.0mg (0.5-1.0ml adrenaline injection 1 in 1000), repeated every 15 minutes until improvement occurs; several times the usual dose may be given if the patient is unconscious. Antihistamines, for example 10mg chlorpheniramine given by a slow intravenous injection, are a useful adjunctive treatment. Intravenous corticosteroids are of secondary value, as their onset of action is delayed for several hours, but they should be used to prevent further deterioration in severely affected patients.

2. Aspirin-Induced Asthma

2.1 Definition and Incidence

In some patients with asthma, aspirin and other nonsteroidal anti-inflammatory drugs precipitate asthmatic attacks. This is a distinct clinical syndrome called aspirin-induced asthma.

About 4% of adult asthmatics give a history of this syndrome, but its frequency is higher (8 to 20%) when oral challenge tests with spirometry are performed (Farr et al., 1978; Stevenson and Mathison, 1975; Spector et al., 1979). There is a clear predominance of females over males exhibiting this syndrome; in children it is very uncommon (Schuhl and Pereyra, 1979; Tan and Collin-Williams, 1982).

Clustering of aspirin intolerance has been described in a few families (Delaney, 1973; Falliers, 1974; Lockey et al., 1973; von Maur et al., 1974; Settupane and Paddupakkam, 1975). However, most

patients with aspirin-induced asthma give a negative family history of both asthma and aspirin intolerance. In our 600 patients with proven aspirin-induced asthma, we found only 2 cases of familial intolerance to aspirin. One was a 19-year-old male whose only brother, also asthmatic, died after taking aspirin. The other was a 21-year-old asthmatic woman whose father had never suffered from asthma but gave a history of angioedema and urticaria without dyspnoea after aspirin ingestion; this was confirmed in a challenge test.

When HLA typing was performed (Jones et al., 1984) no association could be found between any DR antigen, possibly involved with the modulation of the immune response, and aspirin-sensitive asthma.

2.2 Clinical Manifestations and Diagnosis

The sequence of symptoms and the natural history of aspirin-induced asthma are so characteristic that a typical or 'classic' case has been constructed based on a large number of clinical observations (Samter and Beers, 1968). Childhood and adolescence of the aspirin-intolerant patient are not distinguished by any unique features. Beginning with the third or fourth decade of life, the typical patient (women outnumber men 3 to 2) starts to experience intense vasomotor rhinitis characterised by intermittent and profuse watery rhinorrhoea. Over a period of months, chronic nasal congestion appears and physical examination reveals nasal polyps. Bronchial asthma and intolerance to aspirin develop during subsequent stages of the illness. The intolerance presents itself as a unique picture: within an hour after ingestion of aspirin, acute asthmatic attacks develop, often accompanied by rhinorrhoea, conjunctival irritation, and a scarlet flush of the head and neck. Since many patients have taken aspirin in the past with impunity, the initial reaction is usually unexpected and, in fact, quite often not attributed to the drug. These reactions are indeed dangerous; a single therapeutic dose of aspirin or another anticyclo-oxygenase agent can provoke violent bronchospasm, shock, unconsciousness and respiratory arrest (Virchow, 1976).

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The fully developed clinical syndrome has been termed the aspirin-triad (asthma, aspirin intolerance and nasal polyps). Asthma runs a protracted course despite the avoidance of aspirin and cross-reactive drugs. The blood eosinophil count is elevated. Skin tests with common aero-allergens are usually negative; those with aspirin are nearly always negative (Samter and Beers, 1968; Schiavino et al., 1981). Blood histamine levels may rise during the attack, but this is not a consistent finding (Stevenson et al., 1976; Szmidt et al., 1981). An increase in blood neutrophil chemotactic activity roughly parallels aspirin-induced bronchoconstriction (Hollingsworth et al., 1984; Ortolani et al., 1984).

Attempts have been made to measure circulating primary prostaglandins in blood (Asad et al., 1984; Nemoto et al., 1976; Spector et al., 1981). However, it is now clear that this approach can give highly misleading values (Granström and Kindahl, 1984). First, the biological half-life of PGE_2 and $PGF_{2\alpha}$ in the bloodstream is very short, less than 1 minute, and the circulating level is very low; and second, collection and handling of the blood samples generally leads to the artefactual production of prostaglandins and thromboxane, which obscure the true level (Granström and Kindahl, 1984; Roberts and Oates, 1984). It would be most interesting to study eicosanoid metabolism in tissues of the respiratory tract, but this poses great technical difficulties. Slices or homogenates of nasal polyps obtained from aspirin-sensitive asthmatics exhibited increased sensitivity of cyclo-oxygenase to the inhibitory action of aspirin, whereas there was no such increased sensitivity in corresponding tissue samples from patients without aspirin intolerance (Szczeklik et al., 1977b). It has been demonstrated that stimulated alveolar macrophages from aspirin-intolerant asthmatics release smaller quantities of PGE_2 , $PGF_{2\alpha}$ and TXB_2 than do alveolar macrophages from normal subjects (Godard et al., 1982). These studies point to an intrinsic defect of arachidonate metabolism in the respiratory tract of aspirin-intolerant donors. However, such studies are unsuitable for the routine clinical diagnosis of aspirin intolerance, which can

be established with certainty only by aspirin challenge.

Patients are challenged when their asthma is in remission and their FEV_1 is greater than 1.3L. They continue regular medication, including corticosteroids, but stop sympathomimetics and methylxanthines for 10 hours and antihistamines for 24 hours prior to the challenge. Regular intake of sodium cromoglycate and ketotifen should be interrupted 48 hours before the challenge. Aspirin reactions can be blocked by ketotifen (Delaney, 1983; Szczeklik et al., 1980; Wüthrich and Fabro, 1981) and modified by H_1 antihistamines (Szczeklik and Serwońska, 1979). Sodium cromoglycate can alleviate aspirin reactions (Basomba et al., 1976; Martelli and Usandivaras, 1977), though this has not been a uniform experience (Dahl, 1981; Hollingsworth et al., 1984).

All challenges are performed in the morning with a physician present and emergency treatment available. Single-blind placebo challenges with serial spirometric measurements are conducted on the first day (FEV_1 variation should be less than 15%). On the next day aspirin is administered in progressive, incremental oral doses. The starting dose is 20mg. If there is no reaction, the doses are gradually increased until the reaction becomes positive or a dose of 600mg is reached.

The reaction is considered positive if a decrease in FEV_1 (or PEF) greater than 15% occurs, accompanied by symptoms of bronchial obstruction and irritation of nose or eyes. In the absence of these clinical findings the reaction is considered positive only if a fall in FEV_1 (or PEF) greater than 25% is obtained. For relief of adverse symptoms, a β_2 -adrenoceptor agonist can be given by inhalation and, if necessary, aminophylline and steroids can be administered intravenously.

A modification of the challenge tests has been developed in which, instead of giving aspirin by mouth, an aerosol of lysine acetylsalicylate is administered by inhalation (Bianco et al., 1977a; Schmitz-Schumann et al., 1982).

In a few patients, only naso-ocular responses are provoked by aspirin. These patients usually exhibit bronchial asthma at other times. Pleskow et al.,

(1983) recorded this type of reaction in 3 of 50 patients with documented aspirin idiosyncrasy and chronic respiratory tract disease.

In the majority of patients, aspirin intolerance, once developed, remains for the rest of their lives. Repeated aspirin challenges are, therefore, positive, though some variability in intensity of symptoms occurs. However, we and others (Simon et al., 1984) have observed occasional patients in whom positive aspirin challenges became negative after a period of a few years.

2.3 Intolerance to Other Anti-Inflammatory Drugs and Chemicals

In patients with aspirin-induced asthma, not only aspirin but several other anti-inflammatory drugs precipitate bronchoconstriction (table I) [for a recent review see Pleskow et al., 1984]. These include indomethacin, mefenamic, flufenamic and cyclofenamic acids, ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac, piroxicam, sulindac, tiaprofenic acid, aminopyrine, sulphinyprazole, phenylbutazone, zomepirac, tolmetin, diflunisal, fenflumizole and ditazole. All these drugs are contraindicated in patients with aspirin-induced asthma. If necessary, these patients can safely take salicylamide, dextropropoxyphene, benzydamine, guacetisal (guaiacolic ester of acetyl salicylic acid), sodium salicylate, choline salicylate and chloroquine. Paracetamol can also be taken with impunity by the majority of these patients. However, it is safer to give half a tablet first and observe patients for 2 to 3 hours for symptoms. We have found symptoms with paracetamol in 4% of our patients. The rare patients in whom paracetamol produced obstruction to airflow experienced the same effects after ingestion of phenacetin, which is metabolised to paracetamol.

Tartrazine, a yellow azo dye (FD and C No. 5) used for colouring foods, drinks, drugs and cosmetics, induces in some aspirin-sensitive subjects a bronchoconstriction similar to that caused by aspirin and other cyclo-oxygenase inhibitors. In older reports, the frequency of tartrazine cross-reactivity among aspirin-intolerant patients varied widely, ranging from 4 to 50%. This was largely due to

Table I. Tolerance of anti-inflammatory drugs in aspirin-induced asthma

Precipitate attacks of asthma	Well tolerated (cause no bronchoconstriction)
Aspirin	Sodium salicylate
Indomethacin	Choline salicylate
Mefenamic acid	Salicylamide
Flufenamic acid	Dextropropoxyphene
Cyclofenamic acid	Benzydamine
Ibuprofen	Chloroquine
Fenoprofen	Paracetamol ^a
Ketoprofen	
Naproxen	
Diclofenac	
Aminopyrine	
Sulphinpyrazone	
Phenylbutazone	
Piroxicam	
Sulindac	
Tiaprofenic acid	
Zomepirac	
Tolmetin	
Diflunisal	

a When beginning therapy, give half a tablet of paracetamol and observe 2-3 hours for symptoms, which occur in no more than 5% of patients.

differences in the intolerant patients studied. Aspirin intolerance is not a single entity but consists of a number of clinical syndromes with different pathogenesis and symptomatology (Settipane, 1983; Szczeklik et al., 1977a); aspirin-induced asthma is just one of these syndromes.

In a multicentre study performed in collaboration with S. Bianco (Milan) and Ch. Virchow (Davos) we have found tartrazine hypersensitivity in these patients to be rare. Of 168 Italian, Polish and Swiss patients with well documented aspirin-induced asthma, only 4 had positive reactions when challenged with tartrazine (unpublished data). Similarly, Weber et al. (1979) were unable to confirm a single case of tartrazine intolerance among 44 patients, Morales et al. (1985) observed one questionable case in 47 patients, and Stevenson (personal communication, 1984) concluded from extensive clinical experience that intolerance to

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tartrazine is extremely rare among patients with aspirin-induced asthma.

Unlike aspirin-like drugs, tartrazine does not inhibit cyclo-oxygenase activity in sheep seminal vesicles, guinea-pig lung microsomes and human platelets (Gerber et al., 1979). Also, very high concentrations of tartrazine are necessary to interfere with the production of prostaglandins and thromboxanes in guinea-pig lungs perfused with arachidonic acid (Ceserani et al., 1978). It seems, therefore, that cross-sensitivity between tartrazine and aspirin, observed sporadically in aspirin-sensitive asthmatics, is unlikely to be based on prostaglandin inhibition.

Intravenous hydrocortisone may sporadically provoke bronchoconstriction in patients with aspirin-induced asthma. Five such cases have been reported in the literature (for references see Szczeklik and Gryglewski, 1983). Severe wheezing and increased breathlessness, leading even to respiratory arrest, have been observed 1 to 2 minutes after hydrocortisone injection.

Stimulated by these case reports, we studied the effects of intravenous injection of hydrocortisone, as compared with its solvent, in 31 patients with aspirin-induced asthma (Szczeklik et al., 1985b). Mean FEV₁ fell significantly 5 minutes after an intravenous bolus of 300mg of hydrocortisone, but not after the solvent, and returned to the initial values 1 hour later. Only 3 of 31 patients displayed at this time clinical signs of increased impairment of airflow, which resolved spontaneously. Neither in these 3 patients nor in another one, known already to respond with bronchoconstriction to 30 to 50mg of hydrocortisone, did intravenous injections of 20mg methylprednisone, 4mg dexamethasone or 4mg betamethasone produce any signs of bronchial obstruction. Thus, hydrocortisone in several patients with aspirin-induced asthma produced slight, transient and clinically irrelevant impairment of airflow, but it could also lead to definite bronchoconstriction. Though in our patients such bronchoconstrictive reactions resolved spontaneously, they might sometimes be of great clinical concern. It is, therefore, advisable to use steroids other than hydrocortisone in patients with aspirin-

induced asthma. It remains to be seen whether this adverse reaction to hydrocortisone is related to its capacity to reduce prostaglandin generation (Gryglewski et al., 1975) through release of antiphospholipase proteins (Di Rosa et al., 1984).

2.4 Pathogenesis of Aspirin-Induced Asthma

2.4.1 Exclusion of Allergic Mechanisms

Allergic mechanisms for aspirin-induced asthma have been excluded by extensive immunological studies (for references see Schlumberger, 1982; Slepien et al., 1985). Furthermore, in aspirin-sensitive patients, asthmatic attacks may be precipitated by several other analgesics with differing chemical structures, which makes immunological cross-reactivity most unlikely. Non-immunological concepts, which still remain to be proved, include injury to kinin receptors by pre-existing disease which results in their paradoxical stimulation by aspirin (Samter and Beers, 1968), activation of the complement system by aspirin (Voigtlander et al., 1981), and α - β adrenergic imbalance.

Recent studies point to mast-cell degranulation in asthmatic attacks precipitated by aspirin. Indeed, blood neutrophil chemotactic activity increases during the attacks, and roughly parallels bronchoconstriction (Hollingsworth et al., 1984). This, however, appears to be a secondary event, prolonging or amplifying, but not initiating, the reaction (Hollingsworth et al., 1984).

2.4.2 Inhibition of Bronchial Cyclo-Oxygenase

We have put forward an hypothesis (Szczeklik et al., 1975) that in sensitive patients, precipitation of asthmatic attacks by certain analgesics results from inhibition of cyclo-oxygenase, which leads to an imbalance of prostanoids in the respiratory tract. Evidence which has been accumulated in favour of this hypothesis (Pleskow et al., 1984; Szczeklik and Gryglewski, 1983) is as follows:

1) Analgesics with anticyclo-oxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive asthmatics;

2) Analgesics not affecting cyclo-oxygenase lack bronchospastic properties in these patients;

3) There is a fairly good correlation (except for the fenamates) between the potency of analgesics in inhibiting cyclo-oxygenase *in vitro* and their potency in inducing asthmatic attacks in sensitive patients;

4) The degree of enzymatic inhibition which is sufficient to precipitate bronchoconstriction is an individual hallmark (thus, if the threshold dose for any anticyclo-oxygenase drug in a particular patient is known, one can predict the threshold doses for other analgesics in that patient);

5) The enzymatic system generating prostaglandins in nasal polyps of aspirin-sensitive patients has an increased susceptibility to the inhibitory action of aspirin though Nigam et al. (1986) found no change in PGE₂ production.

Are there any exceptions to the hypothesis linking precipitation of attacks by analgesics with their anticyclo-oxygenase activity? Diflalone, an analgesic well tolerated by aspirin-sensitive asthmatics, was thought to be such an exception (Bianco et al., 1977a), but initial reports on the inhibition of cyclo-oxygenase *in vitro* by this drug were not confirmed, and we found diflalone to be devoid of any *in vitro* anticyclo-oxygenase activity. The same applies to sodium salicylate. Paracetamol has no anticyclo-oxygenase activity *in vivo* and is well tolerated in therapeutic doses by the vast majority of aspirin-sensitive asthmatics, but in a rare patient it can produce symptoms of idiosyncrasy. Perhaps these unusual reactions are due to unique properties of paracetamol, which in the presence of high local concentrations of lipid peroxides becomes an inhibitor of cyclo-oxygenase, or perhaps they are due to other non-cyclo-oxygenase-related effects of paracetamol.

For certain pyrazolone drugs it is not easy to draw a simple relationship between *in vitro* and *in vivo* activity, because the potency of these drugs in inhibiting cyclo-oxygenase varies substantially between different human and animal tissues. On the whole, pyrazolones are less potent in this respect than aspirin. This may explain why lower doses of aspirin than of pyrazolones induce bronchoconstriction in sensitive patients. These reactions can now be differentiated from truly allergic ones, hav-

ing an immunological background, and occurring after administration of dipyrone or aminopyrine (Szczeklik et al., 1985a).

Thus, inhibition of bronchial cyclo-oxygenase by aspirin-like drugs appears to set off a chain of reactions leading to asthmatic attacks in aspirin-intolerant patients. What follows at the biochemical level is a matter of speculation. There are two obvious difficulties. Firstly, the target organ of the idiosyncratic reactions is the respiratory tract. It would be, therefore, most fruitful to look at the mediators in the lung substance itself, but technical problems in humans are formidable. Since patients with aspirin-induced asthma have no clinical symptoms suggesting involvement of other organs, it is not surprising that studies of tissues, cells or body fluids outside the respiratory tract were essentially negative (Patrono et al., 1978; Wolfe et al., 1982). Secondly, hypotheses have been constructed based on the current knowledge of arachidonic acid transformations, which is still in its infancy. The potential of several cells for generating diverse, new eicosanoids is enormous, especially during cell to cell interactions: recent evidence has shown that aspirin has an increased inhibitory effect on leucocyte cyclo-oxygenase in aspirin-sensitive asthmatics (Goetzel et al. 1986). More and more families of prostanoids are being discovered. Recently described lipoxins (Serhan et al., 1984) serve as an example. There is no doubt that they can be generated in substantial amounts *in vitro* and that their biological properties predispose them to act as putative mediators. But do they really play a part in human asthma? Thus, the secrets of aspirin-induced asthma are well guarded and difficult to unravel. Based on the anticyclo-oxygenase theory, 4 hypotheses have been put forward (fig. 1):

1) Aspirin-intolerant patients differ from other patients with asthma by depending more on the bronchodilating activity of prostaglandin E₂ than on the β -adrenergic system. Thus, removal of prostaglandin E₂ would lead to dominance of bronchoconstrictor prostanoids, which could not be effectively counterbalanced by the β -adrenergic system (Szczeklik et al., 1975).

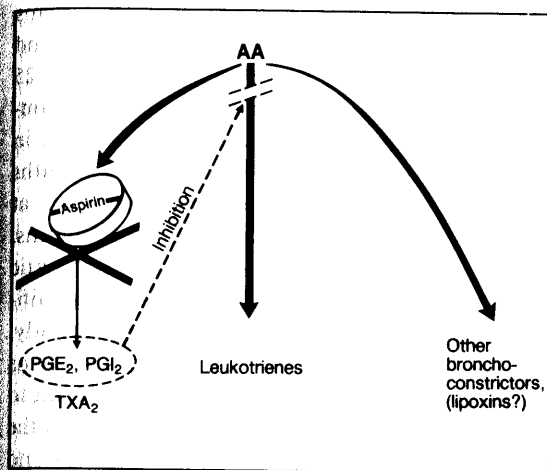


Fig. 1. Aspirin, by blocking cyclo-oxygenase, may lead to bronchoconstriction in sensitive asthmatics, because (1) it deprives their bronchi of bronchodilatory prostaglandins (PGE₂); (2) more arachidonic acid (AA) becomes available for leukotriene generation; (3) a damping mechanism controlling leukotriene production is removed [through lack of PGE₂ and prostacyclin (PGI₂)]; or (4) other unknown bronchoconstrictors are possibly generated (Capron et al., 1985).

2) Prostaglandins E₂ and F_{2α} have opposing effects on human airways, and perhaps aspirin-sensitive asthmatic patients are also unduly sensitive to the bronchoconstrictor prostaglandin F_{2α} and react adversely if synthesis of the bronchodilator prostaglandin E₂ is inhibited more effectively than that of prostaglandin F_{2α} (Settipane and Chafee, 1977). There is little to support this theory (Van Arsdell, 1984). Prostaglandin F_{2α} does not appear to play a significant role in regulating bronchial tone in *in vitro* studies. Furthermore, aspirin-sensitive asthmatic patients are not more sensitive to inhaled prostaglandin F_{2α} than other patients with asthma (Szczeklik et al., 1977c).

3) Aspirin-like drugs, by blocking the cyclo-oxygenase pathway, might divert arachidonic acid metabolism toward leukotrienes C₄ and D₄, which are potent bronchoconstrictors and mucus secretagogues. This concept of shunting arachidonic acid from one pathway to another needs an additional assumption that the airways of aspirin-intolerant patients are more sensitive to leukotrienes than

those of other patients with asthma. If not, all asthmatic patients would react with bronchoconstriction in response to aspirin-like drugs. Obviously, if the 'shunting concept' is right, specific inhibitors of leukotriene biosynthesis should prevent the asthmatic attacks provoked by aspirin. With this aim, benoxaprofen has been used (Lumry et al., 1982) but *in vivo* this drug is a potent inhibitor of cyclo-oxygenase and might even be devoid of any action against leukotriene generation (Salmon et al., 1984). Using a highly specific inhibitor of the 5-lipoxygenase pathway, we were unable to prevent asthmatic attacks provoked by aspirin (unpublished data).

4) Recently, Kuehl et al. (1984) demonstrated that *in vitro* prostaglandin E₂ and prostacyclin (PGI₂) exert a direct inhibitory action on initiation of leukotriene biosynthesis. They reasoned that aspirin-like drugs, by causing a local deficiency of prostacyclin and prostaglandin E₂, might remove a damping mechanism controlling leukotriene production, and release of leukotrienes would result in asthma attacks. If the hypothesis is correct, one might expect that infusions of prostacyclin would offer a protection against asthma precipitated by aspirin. This, however, is not the case (Nizankowska et al. 1986). It seems, therefore, that either the mechanisms described *in vitro* do not operate *in vivo*, or the importance of leukotrienes has been overestimated in this type of asthma.

While these concepts are stimulating for research on the biochemical mechanisms operating in aspirin-induced asthma, they do not reveal the primary cause of these disturbances. We have suggested (Gryglewski et al., 1977) that it could be an infectious agent, e.g. a virus. This is in accordance with the natural history of the syndrome. Aspirin reaction develops in subjects who have never had any difficulty with aspirin before. However, symptoms resembling chronic infection, such as rhinorrhoea and polyposis, usually precede the onset of aspirin intolerance. In this context it is interesting to note that a virus has been recently shown to be able to disturb a specific cell's metabolic functions without causing an overt structural injury (Oldstone et al., 1984).

background, and occurring with dipyrone or aminopyrine.

bronchial cyclo-oxygenase appears to set off a chain of asthmatic attacks in aspirin-intolerant patients. It follows that the biochemical speculation. There are two possibilities, the target organ of the attack is the respiratory tract. It is most fruitful to look at the substance itself, but technical difficulties are formidable. Since patients with aspirin asthma have no clinical involvement of other organs, studies of tissues, cells or the respiratory tract were essential (Goetz et al., 1978; Wolfe et al., 1978; Wolfe et al., 1978). Hypotheses have been advanced, which are still in their infancy. Knowledge of arachidonic acid metabolism, which is still in its infancy, of several cells for generating leukotrienes is enormous, especially interactions: recent evidence that aspirin has an increased effect on cyclo-oxygenase in asthmatic patients (Goetz et al. 1986). Studies of prostanoids are being conducted. Described lipoxins (Serhan et al., 1986). There is no doubt that there are substantial amounts of biological properties predisposing to asthmatic mediators. But do they play a role in asthma? Thus, the sensitivity to aspirin is well guarded. Based on the anticycliclo-oxygenase hypotheses have been put forward.

patients differ from other patients depending more on the amount of prostaglandin E₂ than on the amount of prostaglandin F_{2α}. Thus, removal of prostaglandin E₂ leads to dominance of bronchoconstrictors which could not be effectively counteracted by the β-adrenergic system.

2.5 Prevention and Therapy

Patients with aspirin-induced asthma should avoid aspirin, all products containing it, and the other analgesics listed in table I. But sooner or later, almost every one of us needs aspirin or a related drug for fever, arthritis, chronic headache, or other so-called 'minor' discomforts. What can aspirin-intolerant asthmatics do in that case? They are left with 2 options. Firstly, they can take safely, even for prolonged periods, certain agents which do not inhibit cyclo-oxygenase, like salicylamide, dextro-propoxyphene or benzydamine. Most patients will also tolerate paracetamol or dipyron well. Secondly, they can undergo desensitisation.

This can be achieved by giving 4 to 8 incremental doses of aspirin every 2 to 3 hours under careful observation. The procedure takes 2 days. It starts usually with a dose producing mild adverse symptoms and ends with 600mg aspirin which is then well tolerated. The state of aspirin tolerance (refractory period) lasts 2 to 5 days, but in most patients it can be extended over months, if aspirin is administered regularly at a daily dose of 600mg. At the same time patients can ingest other anti-cyclo-oxygenase drugs without any adverse effects. Refractoriness to aspirin following indomethacin desensitisation has also been observed (Simon et al., 1984). Desensitisation to aspirin is possible in most (Bianco et al., 1977b; Stevenson et al., 1984) but not all (Baldocchi et al., 1983) aspirin-intolerant patients with asthma.

Some patients, studied at La Jolla and San Diego, noted improvement in their underlying chronic respiratory symptoms (naso-ocular responses without asthma) after aspirin desensitisation and during maintenance of the desensitised state (Lumry et al., 1983). Similarly, Chiu (1983) observed that 6 of 12 asthmatic patients, rendered aspirin tolerant and maintained on aspirin, improved when measured by such criteria as the need for anti-asthmatic medication. However, Bianco et al. (1982) noted no such improvement in their patients. Dor et al. (1985), after inducing aspirin tolerance in 9 corticosteroid asthmatics, noted deterioration of lung function in all patients taking

aspirin for more than 1 month. The matter seems to be clarified by the recent first double-blind crossover study, by Stevenson et al. (1984). In 25 desensitised patients there was significant improvement in nasal symptoms and a reduction in use of nasal beclomethasone during the 3 months when they received aspirin treatment. However, at the same time, lower respiratory tract symptoms, values of FEV₁, and the use of anti-asthmatic medication including prednisone were not significantly changed. The results of Stevenson's study, combined with previous clinical observations (Lumry et al., 1983), suggest that desensitisation to aspirin followed by aspirin treatment alleviates the symptoms of rhinosinusitis. On the contrary, no improvement in the symptoms and clinical course of asthma can be expected in the majority of these patients.

Despite being desensitised to aspirin, all patients remain asthmatic. Methacholine and histamine inhalation challenges before and after aspirin desensitisation are unchanged and the patients remain hyperreactive to these agents (Simon et al., 1984). In addition, patients maintained on aspirin, in a desensitised state, still develop asthmatic relapses from all of their prior provoking factors except for aspirin.

The mechanism of desensitisation is unknown. Kowalski et al. (1984) offer the following explanation. Aspirin blocks cyclo-oxygenase irreversibly and a new enzyme must be synthesised to replace molecules inactivated by the drug. After initial cyclo-oxygenase inhibition by aspirin, the original regulatory mechanisms are removed and the functional balance in the bronchi is based on a prostanoic-independent regulatory system. Hypersensitivity to aspirin would then recur with the return of the tissue capacity to generate prostaglandins after aspirin withdrawal.

In summary, desensitisation might be of real benefit to those rare patients who need continuous therapy with nonsteroidal anti-inflammatory drugs (e.g. subjects with rheumatoid arthritis), but who cannot tolerate them. Furthermore, it might be of help in alleviating symptoms of rhinosinusitis. Irrespective of desensitisation, most patients with

month. The matter seems recent first double-blind (Stevenson et al., 1984). In 25 there was significant improvement and a reduction in symptoms during the 3 months of aspirin treatment. However, at the respiratory tract symptoms, the use of anti-asthmatic drugs (prednisone) were not significant. Results of Stevenson's study, and other clinical observations suggest that desensitisation to aspirin treatment alleviates the symptoms. On the contrary, no improvement in symptoms and clinical course was observed in the majority of these

patients treated with aspirin, all patients with atopy, histamine intolerance and after aspirin desensitisation and the patients remain stable (Simon et al., 1984). Patients maintained on aspirin, in a controlled asthmatic relapses provoking factors except for

desensitisation is unknown. We offer the following explanation: cyclo-oxygenase irreversibly cannot be synthesised to replace the drug. After initial treatment with aspirin, the original symptoms are removed and the function of the bronchi is based on a prostaglandin system. Hypersensitivity then recurs with the return of cyclo-oxygenase to generate prostaglandins

Desensitisation might be of real value in patients who need continuous anti-inflammatory drugs (rheumatoid arthritis), but who are not, furthermore, it might be of value in the symptoms of rhinosinusitis. Irritation, most patients with

aspirin-induced asthma need regular therapy to control the symptoms of their disease. The therapy does not differ from that for other types of asthma. Long term treatment with systemic corticosteroids is necessary in at least half of the patients.

3. Asthma Improved by Aspirin

Practising physicians have long been aware of occasional patients with asthma who have claimed that aspirin relieves their shortness of breath. Cases of asthma responding favourably to indomethacin, mefenamic acid, aminopyrine and dipyron have also been reported (for references see Szczeklik and Gryglewski, 1983). It appears now that these patients constitute a distinct subgroup of asthmatics (Szczeklik and Nizankowska, 1983). In all cases, aspirin in a single dose of 0.3 to 1.2g produces bronchodilatation accompanied by reduction in dyspnoea which may last up to 1 day.

This type of asthma has certain features which can be summarised as follows. The disease starts with a flu-like illness, frequently being preceded for years by rhinitis with a watery discharge. The asthma runs a perennial course and is unrelated to seasonal or specific allergenic exposures. Personal and family history of allergy are usually lacking, and skin tests with common aero-allergens are negative. Long term systemic corticosteroid therapy is necessary to control the course of the disease in 50% of these patients.

It is interesting to note that several of the above features are also characteristic of the opposite syndrome, i.e. aspirin-induced asthma. Thus, asthmatic patients who benefit from aspirin are clinically indistinguishable from those in whom aspirin provokes bronchoconstriction.

The striking difference between the 2 clinical syndromes is their response to analgesics. In this respect they are exact opposites. Thus, the same drugs which in these patients produce bronchodilatation, precipitate bronchoconstriction in patients with aspirin-induced asthma. Analgesics inactive in one syndrome are also inactive in the other. Since the active drugs are all anticyclo-oxygenase agents (Vane, 1971), we have suggested

(Szczeklik and Nizankowska, 1983) that pharmacological removal of a product of arachidonic acid cyclo-oxygenation from the respiratory tract of patients responding favourably to aspirin-like drugs helps them to overcome their airway obstruction. Perhaps this product is thromboxane A_2 , prostaglandin $F_{2\alpha}$, prostaglandin D_2 (Hardy et al., 1984), or an as yet unknown metabolite.

Although this syndrome is infrequent and appears to affect 1% or less of adult asthmatics, it is worth bearing in mind by the practising physician, since a trial of aspirin can result in improvement. Proper diagnosis, however, is of vital importance and careful challenge tests with aspirin should always precede commencement of this therapy. This will exclude the risk of bronchoconstriction which might occur in other, clinically indistinguishable, patients with asthma.

4. Urticaria and Angioedema

A survey of adverse skin reactions to analgesics has been published (Stern and Bigby, 1984).

4.1 Intolerance to Aspirin

A few healthy individuals react to aspirin by developing urticarial weals and giant swelling. In addition, many patients with chronic urticaria develop an obvious increase in the weals and swellings after taking aspirin. These 2 groups can be separated, since in the latter, aspirin causes exacerbation of urticaria only while urticaria is active, but does not induce any eruptions in the symptomless period (Michaëlsson, 1969; Warin, 1960). The proportion of patients with chronic urticaria who develop an exacerbation after taking salicylates, usually in the form of aspirin, has ranged from 20 to 40% (Juhlin, 1983; Warin, 1960; Warin and Smith, 1982b). These percentages are similar for aspirin and sodium salicylate (Moore-Robinson and Warin, 1967). Following salicylate administration, blood drug concentrations are high in patients with chronic urticaria (Noid et al., 1974).

A recent survey indicates that aspirin precipitates weals and swelling in patients with idiopathic

urticaria, delayed pressure urticaria and cholinergic urticaria, but not in patients with cold urticaria (Doeglas, 1983). Aspirin may also potentiate the effects of other allergens. Cant et al. (1984) recently described the case of a boy who was known to develop mild angioedema after eating peanuts, but who experienced a life-threatening reaction after ingesting peanuts with aspirin.

It seems clear that all patients with urticaria should avoid aspirin in any form and should exclude from the diet drug additives and colourants (e.g. benzoates or tartrazine) to which some patients are intolerant (Juhlin, 1983; Juhlin et al., 1972). Intolerance to tartrazine has been reported to occur in 8% (Settipane et al., 1976) and 13% (Warin and Smith, 1982a) of patients with chronic urticaria.

The reactions to tartrazine seem to have many features in common with the more frequent reactions to salicylates. Both occur when urticaria is active; when patients have been clear for some time they are able to take salicylates and tartrazine without producing weals. This suggests that the reactions are probably not due to an allergic mechanism but to some pharmacological action (Warin and Smith, 1982a). Avoidance of aspirin and a simple diet free of azo dyes and preservatives may produce improvement in some patients with chronic urticaria (Juhlin, 1983; Rudzki, 1977).

Among those patients who link their cutaneous reactions with aspirin ingestion is a distinct subgroup with type B hypersensitivity to cyclo-oxygenase inhibitors. (Szczeklik et al., 1977a) as opposed to type A (aspirin-induced asthma). The same aspirin-like drugs that induce bronchoconstriction in type A patients also produce angioedema associated with urticaria or rhinitis in type B patients. A few such patients have been described, for example, subjects reacting with urticaria to both ingestion of aspirin and indomethacin (Gryglewski et al., 1975; Matthews and Stage, 1974). Przybilla et al. (1983) recently described a patient who responded with urticaria to challenge with aspirin, indomethacin and dipyron, but not to phenobarbitone or phenacetin; skin tests with all these drugs were negative.

We have studied 17 type B patients. Oral chal-

lenge tests with aspirin were positive in all of them. Similar reactions could be elicited by anticyclo-oxygenase agents, e.g. indomethacin, fenoprofen, ibuprofen and dipyron, but not by drugs without anticyclo-oxygenase properties, e.g. benzydamine, dextropropoxyphene, paracetamol or placebo (Szczeklik et al., 1977a). In 12 patients, these reactions consisted of urticaria and angioedema, the latter being usually limited to the face. In 5 others, angioedema, rhinorrhoea and conjunctival congestion without urticaria developed. There was a clear relationship between the dose of the drug used and the appearance and intensity of the reaction elicited. Pretreatment of one of the patients with ketotifen prevented the appearance of aspirin-induced urticaria and angioedema.

In other patients, impurities contaminating commercial aspirin preparations could be responsible for appearance of urticaria and angioedema (Bundgaard and de Weck, 1975; de Weck, 1971). These contaminants include acetylsalicylic anhydride, acetylsalicylsalicylic acid and cis-disalicylide. Aspirin anhydride is prone to produce salicyloyl and aspiryl conjugates *in vitro*, and to induce the formation of anti-aspiryl antibodies and of contact hypersensitivity in guinea-pigs and rabbits. De Weck (1971) found antibodies directed toward these conjugates in both normal subjects and persons with aspirin-induced urticarial reactions. He has also shown that some patients with repeated urticarial reactions after ingestion of aspirin possess a high degree of skin hypersensitivity specific to aspiryl. These studies point, therefore, to an immunological basis of aspirin hypersensitivity in one subgroup of patients with cutaneous reactions. Impurities present in some commercial preparations of aspirin, but not in others, could explain why certain patients who give a history of aspirin-induced urticaria and angioedema show no reaction when re-challenged with aspirin (Szczeklik et al., 1977a).

4.2 Intolerance to Pyrazolones

Pyrazolone drugs may cause urticaria and angioedema. Though relatively uncommon, these adverse effects occur more often than pyrazolone-

positive in all of them. elicited by anticyclo-methacin, fenoprofen, not by drugs without es, e.g. benzydamine, acetamol or placebo. 12 patients, these re- and angioedema, the o the face. In 5 others, d conjunctival conges- ped. There was a clear e of the drug used and y of the reaction elic- the patients with ke- earance of aspirin- edema. urities contaminating ions could be respon- aria and angioedema 975; de Weck, 1971). acetylsalicylic anhy- acid and cis-disalicy- rone to produce sali- in vitro, and to induce antibodies and of con- a-pigs and rabbits. De s directed toward these jects and persons with actions. He has also th repeated urticarial spirin possess a high ty specific to aspiryl. e, to an immunologi- tivity in one subgroup reactions. Impurities preparations of aspi- l explain why certain of aspirin-induced ur- no reaction when re- eklik et al., 1977a).

ones

use urticaria and an- uncommon, these ad- en than pyrazolone-

linked agranulocytosis. In some patients, bursts of urticaria and angioedema can be followed by anaphylactoid shock (Szczeklik et al., 1985a). The severity of the reactions appears to be determined by individual hypersensitivity and the dose of the drug used. These reactions were discussed in section 1.

5. Other Skin Reactions

Fixed eruptions consist of circumscribed lesions which reappear at exactly the same site each time the drug is taken and subside within a few days after the drug has been stopped. Of the NSAIDs, the pyrazolidines (phenylbutazone, oxyphenbutazone) have been most often incriminated (Fry, 1984; Schulz, 1983). The specificity of the reaction is pronounced. Allergic cross-reactions to chemically related compounds are less common than in other forms of drug allergy such as contact dermatitis. Kennedy et al. (1957) found that 5 of their patients reacted to aminopyrine and not to closely related pyrazolones. Rarely, double or triple sensitisation occurs at separate skin sites. In a large series comprising 484 cases, Furuya et al. (1966) found double sensitisation to barbitone and aminopyrine in 2 patients.

Lyell's syndrome (toxic epidermal necrosis) is characterised by high fever, leucocytosis, anaemia and development of large bullae in the areas of skin already affected by macular eruptions. The bullae rupture and the appearance resembles that of a second-degree burn. Although it is generally accepted that drugs are the most common cause of Lyell's syndrome, a number of agents, particularly analgesics, may have been used for prodromal symptoms and may, therefore, have been unjustly incriminated (Rasmussen, 1980). Pyrazolidines (Schulz, 1983) and salicylates (Gérard et al., 1982) are the most often incriminated NSAIDs, and a few reports have named fenbufen and indomethacin. A fatal case following piroxicam treatment has also been described (Roujeau et al., 1981). Mortality in the generalised, drug-induced form of the syndrome amounts to 30% (Schulz, 1983). Differentiation of the drug-induced form from staphylococcal Lyell's syndrome is important for prognosis and therapy. Besides the history of the

disorder, isolation of staphylococci from the nose, throat and skin lesions helps in differentiating these 2 forms of the syndrome.

In *erythema multiforme* symmetrical eruptions of varying morphology appear, usually on the upper extremities (Fry, 1984). In the mild form, no treatment is required and the disease is self limiting. In the more severe forms, particularly *Stevens-Johnson syndrome*, systemic corticosteroids are administered and hospitalisation is necessary. Nine cases of Stevens-Johnson syndrome have been associated with diflunisal (Vaneček, 1983); sporadic cases in patients treated with pyrazolones have also been described (Fry, 1984).

Purpura on the legs has been recorded following phenylbutazone (Fry, 1984) or aspirin (Della Torre et al., 1981). The mechanism involved may be allergic vasculitis or thrombocytopenic purpura.

Lichen planus-like eruptions similar to lichen planus, but usually more confluent, have been linked to aminophenazone (Fry, 1984).

Photodermatitis is a well recognised complication of treatment with several non-steroidal anti-inflammatory drugs. Naproxen, piroxicam and tiaprofenic acid were demonstrated to induce phototoxic reactions both *in vitro* and *in vivo* (Diffey et al., 1983). Benoxaprofen has frequently been associated with photosensitivity reactions, particularly in fair-skinned people; this contributed to its withdrawal from the market in some countries. Blisters appear shortly after exposure to strong sunshine. Skin manifestations resemble porphyria cutanea tarda, but there is no demonstrable abnormality of haem synthesis (Howard et al., 1985). Immunofluorescence studies reveal immunoglobulin G and C₃ deposition around the vessels and patchy and granular immunoglobulin deposition at the dermoepidermal junction. Upon withdrawal of the offending analgesic, blistering and skin fragility cease within a few weeks.

6. Intolerance to Analgesics in Lupus Erythematosus

Hypersensitive reactions to drugs are frequently observed in patients with systemic lupus erythematosus, and analgesics are no exception.

In 8 patients with systemic lupus erythematosus who developed adverse reactions to ibuprofen (Mandell et al., 1976; Sonnenblick and Abraham, 1978; Szczeklik et al., 1977a), sudden appearance of high fever, abdominal pain and rash was reported. Serum transaminases were raised in some patients. These reactions do not appear to result from inhibition of cyclo-oxygenase. Perhaps, like many other clinical manifestations of lupus erythematosus, they are due to the formation of antigen-antibody complexes.

7. Analgesics and Mastocytosis

In patients with severe systemic mastocytosis, the addition of aspirin to the antihistamine regimen is warranted, although under strictly controlled circumstances (Lewis, 1984). Oates and his colleagues (Roberts et al., 1980; Turk et al., 1983) have proved the therapeutic value of aspirin in such patients and have demonstrated that it is effective because it blocks synthesis of prostaglandin D₂ from the mast cells. However, some patients with mastocytosis have a severe hypotensive response to initial ingestion of aspirin and other cyclo-oxygenase blockers, even to the point of frank shock or, rarely, death (Waldenström, 1980). Thus, the first aspirin dose should be administered only during maintenance therapy with H₁ and H₂ receptor antagonists (e.g. chlorpheniramine maleate, 8mg, 4 times daily and cimetidine, 300mg, 4 times daily). The initial dose of aspirin should not exceed 20mg 4 times daily and should then be doubled every 1 to 2 days until the therapeutic dose is reached. The warning that other drugs that inhibit cyclo-oxygenase have to be considered just as potentially dangerous (and just as potentially therapeutic) as aspirin should be strongly heeded.

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