

Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis

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Clinical observations coupled with challenge tests using 16 different nonsteroidal anti-inflammatory drugs were carried out in 123 patients with a history of allergy to analgesics. Several different patterns of hypersensitivity could be distinguished. Our clinical and experimental data suggest that in the largest group of patients studied the idiosyncrasy to aspirin-like drugs was not of immunologic type but was due to the suppression of prostaglandin generation in tissues of the patients. The adverse reactions to aspirin-like drugs were manifested as asthmatic attacks or urticaria/angioedema. In another group, the hypersensitivity was limited to pyrazoline drugs and was not related to inhibition of prostaglandin biosynthesis. This type of hypersensitivity, resulting in anaphylactic shock and urticaria, seems to have an immunologic background. In a patient with lupus erythematosus the hypersensitive reactions to analgesics were related neither to their chemical structure nor to their known biochemical activities. In a small group of patients the hypersensitivity to aspirin could possibly be attributed to the minute amounts of impurities present in some commercial products.

Aspirin, probably the most common medication in the world today, is well tolerated by the majority of people. First idiosyncratic reactions to aspirin, however, have been recognized soon after its introduction into therapy, and a recent large survey¹ listed aspirin among ten drugs most frequently involved in adverse reactions. The concern about the dangerous response of some patients to aspirin has increased when it was realized that similar responses might occur following ingestion of other nonsteroidal anti-inflammatory drugs. Many of those have also valuable antipyretic and analgesic effects, therefore being alternatively called nonnarcotic analgesics. Generally, nonsteroidal anti-inflammatory drugs comprise a large group of so called aspirin-like drugs, the therapeutic action of which is closely related to the inhibition of prostaglandin biosynthesis,^{2, 3} and a smaller group of analgesics with an unknown mechanism of action (Table I). The number of new analgesics is con-

stantly being augmented by pharmaceutical research.⁴

Adverse reactions to analgesics result in severe asthmatic attacks, urticaria, angioedema, or shock. Thus, the major symptoms resemble those of an allergic disorder of immediate type. On the contrary, cytotoxic reactions against individual organs occur rarely. In these cases, the target sites include blood cells,⁵⁻⁷ liver,⁸ or kidney.^{8, 9}

Clinical symptomatology of the adverse reactions to nonsteroidal anti-inflammatory drugs varies greatly from patient to patient, and their pathogenesis is poorly understood. Recently, however, we put forward a hypothesis^{10, 11} that one type of hypersensitivity to aspirin-like drugs, occurring in bronchial asthma, can be explained by the biochemical blockade of generation of bronchodilator prostaglandins of the E series in the respiratory tract of hypersensitive asthmatics. Here we report that among patients with hypersensitivity to analgesics various clinical patterns can be distinguished. We present also experimental data suggesting that this variety of clinical patterns reflects a variety of the pathogenetic mechanisms by which the adverse reactions to analgesics are precipitated.

PATIENTS AND METHODS

The study included 123 patients, 51 men and 72 women, referred to this Department with complaints of allergic reactions to aspirin-like drugs. Their ages ranged from 16 to 68.

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TABLE I. Effect of nonsteroidal anti-inflammatory drugs on PG synthesis

Drugs	Producer	Effect on PG synthesis	IC ₅₀ (μM)*
Aspirin	Polfa	Inhibition	176
Indomethacin	Polfa	Inhibition	0.10
Mefenamate	Parke, Davis & Company	Inhibition	0.25
Flufenamate	Parke, Davis & Company	Inhibition	15
Phenylbutazone	Polfa	Inhibition	148
Fenoprofen	Eli Lilly and Company	Inhibition	55
Ibuprofen	The Upjohn Company	Inhibition	50
Noramidopyrine	Polfa	Inhibition	500
Aminophenazone†	Polfa	Stimulation or inhibition	—
Diclofenac	Ciba-Geigy Corporation	Inhibition	0.15
Naproxen	Syntex Research	Inhibition	14
Dextropropoxyphene	Eli Lilly and Company	No effect	—
Salicylamide	Polfa	No effect	—
Benzylamine	Polfa	No effect	—
Paracetamol†	Polfa	Stimulation or inhibition	—
Chloroquine	Polfa	No effect	—

*Concentration of a drug which inhibits the activity of microsomal PG synthetase from bovine or ram seminal vesicles by 50%. The data were obtained using the method described by Gryglewski.¹⁴

†Stimulation of PG synthesis occurs when exogenous cofactors are omitted from the microsomal preparation. A weak inhibition of PG generation (IC₅₀ > 1,000 μM) has been observed when the enzymic preparation is supplemented with exogenous glutathione and hydroquinone.¹⁵

TABLE II. Clinical background of the patients studied

	Hypersensitivity to PG synthetase inhibitors		Allergic idiosyncrasy to pyrazoline drugs	Chronic urticaria aggravated by both aspirin and placebo	Patients with history of urticaria/angioedema following aspirin intake, unproved during oral challenges with both aspirin and placebo
	Type A (asthmatic attacks)	Type B (urticaria/angioedema)			
Number of patients	80	10	15	13	14
Mean age in years	41	41	36	34	30
and range	(16-68)	(20-58)	(17-52)	(26-49)	(16-49)
Male/female	34/46	3/7	3/12	7/6	4/10
Bronchial asthma	80	2	3	2	5
Family history of atopy	18	1	7	1	3
Positive skin tests to inhalant allergens	16	1	7	1	2
Nasal polyps	49	Not found		Not found	

The methods in oral challenge tests were described previously.^{11, 12} These tests consisted of 4-hr registration of peak expiratory flow (PEF) and clinical observation over the 24-hr period following ingestion of the drug studied. After obtaining a written consent, the tests were begun with the smallest dose of a drug. If no response occurred, the doses were increased at the next challenge until the reaction became positive or a dose equivalent to that in 1 to 2 tablets was reached. In assessment of bronchopulmonary effects of the drugs studied, a decrease in PEF of 16%-25% was con-

sidered positive if accompanied by clinical symptoms of bronchial obstruction and by appearance of either rhinorrhea or profuse lacrimation. In the absence of these symptoms, the reaction was considered positive only if fall in PEF of more than 25% was obtained. Lactose at a dose of 100 mg was used as placebo. Uncomfortable symptoms were relieved by β₂-adrenoreceptor stimulants or antihistaminics. In a few patients in whom insufficient improvement was obtained, aminophylline, calcium, or hydrocortisone was administered intravenously. In the oral challenge

TABLE III. Aspirin-induced asthma—results of the oral challenge tests

Drug	Dose range (mg)	Minimal induction dose in majority of patients (mg)	No. of patients studied	No. of patients with positive reaction
Aspirin	20-300	40	80	80
Indomethacin	2-30	5	38	38
Fenoprofen	20-200	40	32	32
Ibuprofen	50-400	50	31	30
Naproxen	30-100	40	11	11
Diclofenac	10-40	10	14	12
Noramidopyrine	50-2,000	200	22	22
Mefenamic acid	50-250	250	16	10
Flufenamic acid	50-300	200	14	9
Phenylbutazone	200-400	200	26	11
Paracetamol	150-600	300	49	3
Salicylamide	500-1,000		29	0
Dextropropoxyphene	65-130		41	0
Benzydamine	50-100		77	0
Chloroquine	250-500		23	0
Placebo (lactose)			80	0

tests 16 analgesic drugs were used. Most of them, similarly to aspirin, inhibit prostaglandin (PG) synthetase; however, few others have no effect on the enzymic generation of PGs while still others stimulate PG biosynthesis. Since these biochemical effects of analgesics have been found meaningful for their capability to produce adverse reactions in hypersensitive patients,¹³ we have summarized our experimental data on the influence of these analgesics on PG biosynthesis in vitro (Table I).

RESULTS

Aspirin-induced asthma

This group consisted of 80 asthmatic patients (Table II) who all developed symptoms of obstruction to airflow and a fall in PEF following oral challenge with aspirin. The average decrease in PEF was 44%. In 60 patients the hypersensitivity had appeared a few years after the onset of asthma. Chronic rhinitis was common in all of the patients. Intolerance to drugs other than analgesics was reported by 20 patients. Penicillin and sulfonamides were most frequently listed.

Fifteen aspirin-like drugs were used in oral challenge tests. The results are summarized in Table III. PG synthetase inhibitors, namely aspirin, indomethacin, fenamates, fenoprofen, ibuprofen, diclofenac, naproxen, noramidopyrine, and phenylbutazone, all precipitated asthmatic attacks. On the contrary, the drugs not affecting PG generation, such as dextropropoxyphene, salicylamide, benzydamine, and chloroquine (Table I) caused no reaction.

We have noted previously¹¹⁻¹³ that those patients in whom low doses of aspirin precipitated adverse reaction also responded to low doses of indometha-

cin, fenoprofen, and ibuprofen, while those who developed obstruction to airflow only following relatively high doses of aspirin also needed high doses of the above PG synthetase inhibitors. These observations were now extended to another PG synthetase inhibitor causing bronchospasm. Thus, in 2 of 22 patients challenged with noramidopyrine, the positive reaction could only be elicited with a very high dose of the drug, namely, 2,000 mg (equivalent to 4 tablets). The same 2 patients had also very high threshold of sensitivity to aspirin (250 and 300 mg). Comparison of the minimum doses of aspirin causing positive reactions in each of 22 patients with those of noramidopyrine revealed a positive correlation ($r = +0.93$, $p < 0.001$).

In 8 patients oral challenge tests with aspirin were repeated after 1 to 3 yr of intensive treatment of their asthma. Five of these patients who entered complete remission needed now 1 to 3 times higher doses of aspirin to induce positive reaction. On the contrary, in 3 other patients, whose clinical condition has remained unchanged, the threshold doses of aspirin-inducing bronchospasm remained the same. Thus, the results of repeated oral challenge tests might reflect the dynamics of the disease.

Twelve patients with aspirin hypersensitivity, who required prolonged corticotherapy to control their asthma, were given disodium cromoglycate for 6 to 24 mo in a daily dose of 60 to 80 mg. As a result of this treatment, 4 of them were able to stop taking steroids altogether; in 2 about 50% reduction of the dose of steroids was achieved, while 6 others remained on the same dose.

Urticaria and angioedema associated with aspirin intake

Thirty-seven patients had been evaluated because of history of urticaria and angioedema associated with ingestion of aspirin. According to the results of challenge tests they could be further divided into 3 groups.

The best-distinguished group was formed by 10 patients (Table II). Some of them reported that appearance of intolerance to aspirin-like drugs was preceded by acute infection (flu-like illness, 2; cholecystitis, 2; pyelitis, 1; adnexitis, 1). They all had positive reactions to aspirin. Similar reaction could also be elicited by other PG synthetase inhibitors, e.g., by indomethacin, fenoprofen, ibuprofen, and noramidopyrine, but not by benzydamine, detropropoxyphene, paracetamol, or placebo (Table IV). In 7 patients, these reactions consisted of urticaria and angioedema, the latter being usually limited to the face. In 3 others, angioedema, rhinorrhea, and conjunctival injection without urticaria developed. There was a clear relationship between the dose of the drug used and the appearance and intensity of the reaction elicited (Table IV). The cutaneous reactions described developed usually later (90 min to 12 hr) following the challenge than bronchospastic response in the group of aspirin-sensitive asthmatics (30 min to 4 hr) subjected to similar challenges. Measurement of PEF revealed no significant changes in the group studied, except for 3 challenges performed in 2 patients. In 1 patient following fenoprofen, and in another following both fenoprofen and noramidopyrine challenges, shortness of breath, wheezing, and fall in PEF occurred. These symptoms, never experienced by the patients before, lasted about a half hour and subsided spontaneously. They did not reappear during the next 6-mo observation period.

The second group consisted of 14 patients in whom diagnosis of aspirin intolerance could not be confirmed.

In the third group, comprising 13 patients, none of whom was known to have intolerance to milk, exacerbation or appearance of wheals and giant swellings was observed shortly after taking both aspirin and placebo. These effects were more noticeable during phases when underlying urticarial tendency was greater. They did not, however, appear to depend on dose of aspirin or placebo. Thus, increase in dose was not accompanied by increase in cutaneous response.

Patients with idiosyncratic reactions to pyrazoline drugs but not to aspirin

Anaphylactic shock following administration of noramidopyrine or aminophenazone was the reason

for hospital administration in 13 of 15 patients forming this group (Table II). The shock was often accompanied by generalized urticaria and syncope. In 3 persons the unconsciousness lasted several minutes. Other common symptoms included: angioedema, maculopopular rash, fever, and transitory arthritis. Serum IgE level was elevated in 6 of 9 patients.

Because of fear of generalized reactions, challenge tests were limited to 2 patients who reported only urticaria after pyrazoline drugs. In one, half an hour after ingestion of 50 mg of noramidopyrine generalized urticaria and fall in blood pressure occurred. In another, urticaria developed after 20 mg aminophenazone; 20 mg noramidopyrine was without effect, but 50 mg produced single eruptions of urticaria type.

In 14 of 15 patients skin tests with noramidopyrine and aminophenazone were carried out within 2 to 12 mo after the acute adverse reaction had taken place. The drugs were always introduced first by the scarification method, and in case of negative results, they were injected intracutaneously. The results were positive in all of the patients tested. Stronger reaction was usually elicited with this drug, which was indicated by the history as the reason for acute adverse reaction. For comparison, the same intracutaneous tests with noramidopyrine were performed in 18 patients with aspirin-induced asthma. In all of the patients except one, the results were negative.

Since the patients with idiosyncrasy to pyrazoline drugs gave a history of good tolerance of aspirin, they were all subjected to the challenge tests with increasing doses of the following drugs: aspirin up to 1,000 mg, indomethacin up to 25 mg, and paracetamol up to 600 mg. None of these drugs caused any adverse reaction in the patients studied.

Hypersensitivity in lupus erythematosus

We have seen a 46-yr-old man with a diagnosis of lupus erythematosus in an early stage, who developed severe adverse reaction to analgesics. For about a year preceding admission to the hospital, he received several short-term treatments with aspirin-like drugs because of arthralgia. Each time the joint pains were relieved, but spiking fever and chills developed repeatedly. Twenty-four hours before entering the hospital he started taking aspirin and mefenamic acid because of muscle and joint pain. On admission he was in shock, complaining of abdominal cramps. Blood pressure was 70/50 mm Hg, temperature, 41.2° C, and generalized erythema of skin was present. He was treated with high doses of hydrocortisone and antihistaminics, and his symptoms subsided within a few days.

TABLE IV. Type B hypersensitivity to inhibitors of prostaglandin biosynthesis

Patient	No.	Symptoms	Drugs (doses expressed in mg)				
			Aspirin	Indomethacin	Fenoprofen	Ibuprofen	Noramidopyrine
J. K.	1	Urticaria and angioedema	30- 50+ 150+		50- 300+		50- 150- 500-
A. G.	2	Urticaria and angioedema	50- 200+	5- 15+	50+	50- 150+	50- 150- 500-
U. G.	3	Urticaria and angioedema	50- 150+	5- 10+	50- 150+	150- 300- 450+	50- 150- 500+
J. K.	4	Urticaria and angioedema	100- 300+	10+		500+	500+
H. K.	5	Urticaria, maculopopular rash, and angioedema	50- 100+	5- 10+	50- 150- 300-	150- 300-	50- 150- 500- 1,500+
W. G.	6	Urticaria, maculopopular rash, and angioedema	50- 100+	5- 10+	50+		50- 100- 200- 500+
A. N.	7	Angioedema, rhinitis	50- 100+		50- 150+		
K. K.	8	Angioedema rhinitis	50- 100- 300- 600+				500- 1000- 2,500+*
G. Z.	9	Conjunctivitis, rhinitis, and edema of eyelids	50- 100- 250+	5- 10- 25+			50- 150- 500- 2,500+*
R. K.	10	Conjunctivitis, rhinitis, and edema of eyelids	50- 100+	5- 10+	50- 100+		50- 100+ 300+

In all 10 patients no reaction could be elicited with benzydamine 50 mg, dextropropoxyphene 65 mg, paracetamol 300 mg, or placebo.
-: Lack of reaction. +: Reaction positive.

*Intravenous injection.

The challenges with aspirin 20 to 600 mg, indomethacin 1 to 25 mg, noramidopyrine 20 to 600 mg, and aminophenazone 10 to 300 mg were all negative. Ingestion of phenylbutazone 50 mg led to appearance of rash and elevation of temperature up to 38.5° C. One hour after taking 40 mg mefenamic acid, pruritus with erythema of face and chest appeared and temperature rose to 39.2° C, blood pressure fell to 90/70 mm Hg, and the patient was complaining of abdominal and back pain. He received hydrocortisone and antihistaminics, and the symp-

toms subsided completely 2 days later. Although ibuprofen was indicated by the patient as causing similar reaction, the challenge was not performed.

DISCUSSION

Based on characteristic clinical picture and a specific response to nonsteroidal anti-inflammatory drugs, the following types of hypersensitivity could be distinguished: (1) hypersensitivity to PG synthetase inhibitors (aspirin-like drugs), manifested clinically as asthmatic attacks and urticaria/angioedema,

(2) allergic idiosyncrasy to pyrazoline drugs; and (3) hypersensitivity to some analgesics in lupus erythematosus.

Aspirin-sensitive asthma has already been recognized by others as a separate clinical syndrome. In fact, the sequence of symptoms and the natural history are so characteristic that a typical or "classic" case has been constructed.^{16, 17} In such a case, the consecutive stages of the disease, covering often the period of several years, include: vasomotor rhinitis, nasal polyposis, bronchial asthma, and, finally, appearance of a unique intolerance to aspirin, characterized by the precipitation of asthmatic attacks. Little can be added to this natural history and other clinical symptoms,^{17, 18} which were well reflected among our patients.

Our observations, however, indicate that all tested aspirin-like drugs can be as harmful as aspirin to the sensitive asthmatics. The criterion for precipitation of the asthmatic attack by a drug is its potency to inhibit PG biosynthesis and not the similarity of its chemical structure to aspirin. There exists a fairly good correlation between potencies of aspirin-like drugs to inhibit PG synthetase *in vitro* (Table I) and to induce asthmatic attacks in sensitive patients (Table III), except for fenamates (mefenamic and flufenamic acids). Fenamates have been reported to antagonize the bronchoconstrictor action of $\text{PGF}_{2\alpha}$.¹⁹ It well may be that this "side effect" of fenamates is responsible for the fact that these potent PG synthetase inhibitors are relatively weak inducers of asthmatic attacks in sensitive patients. It is noteworthy to observe that noramidopyrine cannot replace aspirin as an analgesic in aspirin-sensitive asthmatic patients,²⁰ since this drug, though weakly, still inhibits PG synthetase and thereby at a high dosage it is dangerous for these patients. If necessary, they can be treated with salicylamide, dextropropoxyphene, benzydamine, or chloroquine, the drugs that have little or no effect on PG biosynthesis (Table I).

Many of these patients need prolonged corticotherapy to control their asthma. It therefore seems interesting that in 6 of our 12 patients the use of disodium cromoglycate resulted in clinical improvement and permitted reduction or even discontinuation of long-lasting corticotherapy. This is in line with recent observations indicating that in some aspirin-sensitive patients bronchoconstriction induced by aspirin can be prevented by prior short administration of disodium cromoglycate.²¹⁻²³ The therapeutic value of disodium cromoglycate here reported needs confirmation on a larger group of patients.

Inhibition of PG biosynthesis seems also to be in-

involved in pathogenesis of urticaria/angioedema in one subgroup of patients who link their cutaneous reactions to aspirin ingestion. We call this type B hypersensitivity to PG inhibitors as opposed to type A (aspirin-sensitive asthma). Such a subgroup could be distinguished clearly from all other patients with skin reactions to aspirin studied by us. It should be noted that Settupane and Padupakkam²⁴ recently described two types of aspirin intolerance, depending on results of oral challenge tests with this drug. One was characterized by bronchospasm, the other by urticaria/angioedema. These authors thought that the two different responses might be due to two different, yet unknown, mechanisms. Our observations confirm the existence of these two different types of response to aspirin but suggest that a similar mechanism operates in both types. Thus the same aspirin-like drugs that induced bronchoconstriction in type A patients also produced angioedema associated with urticaria or rhinitis in type B patients. All of the drugs causing positive reactions in both groups A and B were inhibitors of PG biosynthesis, indomethacin being the most powerful of them in this respect (Table I). It is therefore interesting to note that single patients have been described recently in whom both ingestion of aspirin and indomethacin led to urticaria.^{25, 26} Similarly, of several different drugs studied by Doeglas,²⁷ indomethacin most frequently induced cutaneous reactions in patients with urticaria and hypersensitivity to aspirin. On the other hand, analgesics that do not inhibit PG biosynthesis could be ingested without any untoward reactions by those of our patients who had previously responded with urticaria to aspirin and indomethacin. Our suggestion of similar prostaglandin mechanism underlying the two clinically different reactions is further supported by the presence of both of these reactions in the same patients. Thus, it has been well documented^{16, 18, 28} that in certain sensitive asthmatics, precipitation of bronchoconstriction by aspirin is accompanied by angioedema, rhinitis, or urticaria. At least 8 of our 80 asthmatics developed this type of reaction. Scarlet flush beginning in the scalp and spreading downward to the chest and shoulders is relatively common in aspirin-induced bronchoconstriction, and it has also been observed in patients responding with urticaria to aspirin ingestion.²⁷ Furthermore, we have noticed that in 2 of our 10 type B patients who had developed urticaria after fenopropfen and noramidopyrine, transitory wheezing and fall in spirometric values occurred as well. These two patients had never suffered from asthma.

On the basis of our results we suggest that hypersensitive reactions to aspirin-like drugs (i.e., to PG

synthetase inhibitors), which can be manifested as asthmatic attacks (type A hypersensitivity) or urticaria and angioedema (type B hypersensitivity), are not of immunologic origin. Instead, we propose that the inhibition of PG biosynthesis by these drugs is responsible for the untoward reactions. More specifically, we postulate that it is the blockade of generation of prostaglandins of the E series (PGEs) which accounts mainly for the idiosyncrasy to aspirin-like drugs. PGEs are not only bronchodilators^{29, 30} but also stabilize histamine stores in mastocytes.^{13, 31, 32} We speculate that PGEs may play a special role in preserving integrity of mastocytes in the respiratory tract of patients with type A hypersensitivity, while in patients with type B hypersensitivity cutaneous mastocytes are more susceptible to the stabilizing effects of PGEs. Thus, the removal of PGEs by aspirin-like drugs is followed by a release of histamine from mastocytes either in respiratory tract or in skin. Histamine can initiate the local generation of several other chemical mediators (e.g., thromboxane A₂, slow-reacting substance A, kinins),³³ which, along with histamine, finally cause either asthmatic attack or skin reactions. The concept here presented gets additional support from the results of recent studies in which aspirin-sensitive asthmatic subjects were found to differ from the controls by increased susceptibility to inhibitory action of aspirin on PG synthesis in nasal polyp tissues,³⁴ by increase of plasma histamine levels following oral challenge with aspirin,³⁵ and by vivid bronchial response to histamine and PGE.³⁰

The group just described (type B hypersensitivity) represents only a fraction of patients who report aspirin among factors precipitating their urticaria. The incidence of aspirin hypersensitivity in chronic urticaria is high and has been reported as varying from 21% to 75%.^{36, 37} It has been noticed previously^{37, 38} and confirmed in this study that in many of these patients aspirin worsens the already existing urticaria but does not induce any eruptions in symptomless periods. These exacerbations of existing urticaria are difficult to explain on an allergic basis. Warin³⁸ thought that perhaps in these patients aspirin acted as a liberator of histamine. This explanation would not, however, account for aggravation of existing urticaria by placebo as was the case with our patients.

Still another group to be differentiated from urticaria/angioedema induced by PG biosynthesis inhibitors is formed by patients who give the history of aspirin-induced urticaria and angioedema, but in whom the results of challenge tests with aspirin are negative. Impurities present only in some commercial preparations of aspirin could explain this bizarre

phenomenon. Perhaps these patients are allergic to aspirin anhydride, a contaminant of some acetylsalicylic preparations.^{39, 40} In such patients the anaphylactic-type reactions to aspirin might be mediated by the reagins of IgE type.⁴¹

There is a group of patients who are hypersensitive to analgesics of the pyrazoline group but not to the aspirin-like drugs. These patients, more often than those with hypersensitivity to PG inhibitors, had a family history of allergic diseases and positive skin tests to common allergens. Their serum IgE levels are also often elevated. The untoward reactions to pyrazoline compounds can be highly dangerous, since they result often in anaphylactic shock. The immunologic basis for hypersensitivity to noramidopyrine and aminophenazone is suggested by lack of any relation between the effects of these drugs on prostaglandin biosynthesis and their clinical effects in hypersensitive patients. Noramidopyrine is a weak inhibitor of prostaglandin biosynthesis, while aminophenazone stimulates the generation of prostaglandins (Table I). On the other hand, aspirin and paracetamol (chemically unrelated to pyrazoline drugs) influence prostaglandin biosynthesis in a similarly opposing manner as noramidopyrine and aminophenazone (Table I); however, neither aspirin nor paracetamol induces adverse reactions in patients hypersensitive to the pyrazoline compounds. Therefore, we believe that the selective hypersensitivity to pyrazoline analgesics has an immunologic background and is unrelated to the effects of these drugs on prostaglandin generation.

Drug sensitivity reactions are frequently observed in patients with lupus erythematosus but are not usually caused by analgesics. In our patient, mefenamic acid, phenylbutazone, and possible ibuprofen, but not several other aspirin-like drugs, were involved in severe reactions of which high fever was a leading symptom. It is interesting that similar febrile reaction associated with administration of ibuprofen has been observed recently in two patients with lupus erythematosus.⁴² Perhaps these reactions, similarly to many other clinical manifestations of lupus erythematosus, result from formation of antigen-antibody complexes. From the practical point of view, mefenamic acid and ibuprofen should be considered as possible fever-inducing factors in patients with lupus erythematosus who have recently taken these drugs.

Hypersensitive reactions to analgesics are a complex phenomenon. In the largest group of patients studied by us, such reactions were not of immunologic type but were closely related to the enzymic inhibition of PG synthetase by aspirin-like

Progenes
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drugs and manifested themselves as asthmatic attacks or cutaneous reactions. On the other hand, some patients were hypersensitive only to pyrazoline compounds but not to aspirin-like PG synthetase inhibitors. This type of hypersensitivity, resulting in anaphylactic shock and urticaria, seems to have an immunologic background. The above groups do not cover all possibilities of hypersensitivity to nonsteroidal anti-inflammatory drugs. In some patients, e.g., those with lupus erythematosus, still other pathogenetic mechanisms seem to operate.

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