

From the hospital for contagious diseases, Stockholm, Sweden.
(Head: Justus Ström)

THE ROLE OF DRUGS IN CERTAIN FEBRILE
MUCOCUTANEOUS MANIFESTATIONS
(SYNDROMA MUCOCUTANEUM FEBRILE) AS
ILLUSTRATED BY PROVOCATION OF CLINICAL
AND THROMBOCYTE REACTIONS

By

JUSTUS STRÖM

Allergic exanthemas caused by drugs have become quite common with the enormous increase in our therapeutic arsenal, especially as many of the new drugs are allergenically potent. On the other hand many infections may give rise to an exanthema which is not a normal symptom of the disease but a reaction particular to the individual. Less well known is the fact that the mucosa especially in the orifices of the body may be involved in the allergic reaction in a multitude of ways.

These problems have been studied for fifteen years, particularly the severe forms of febrile mucocutaneous syndromes which go by many names (*Erythema exudativum multiforme pluriorificialis sive major* (1), *Ectodermosis erosiva pluriorificialis* (5), *Rendu-Fiessinger's syndrome* (5, 6), *dermatostomatitis* (2), *Stevens-Johnson disease* (9), *mucocutaneous ocular syndrome* (7), *mucocutaneous respiratory syndrome* (8).

These various syndromes may be different forms of an allergic reaction. This opinion was advanced in 1948 (10), and in 1956 was further supported by experimental evidence in studies of probenecid-penicillin allergy (11), in which exanthema and fever combined with various mucosal manifestations were provoked.

Thus there is no question of separate diseases but a syndrome developed in various ways. The designation *Syndroma mucocutaneum febrile* entirely covers the symptomatology. For the diagnosis to be made there must be fever, exanthema, and involvement of at least two orifices. In barely onethird of the cases is the exanthema of the multiform exudative type, it is usually a maculopapulous, often symmetric, haemorrhagic eruption, but may also be morbilliform and scarlatiniform. The orifices exhibit different degree of inflammatory processes, being frequently membranous and ulcerous. The fever is often high and lasts on an average one week.

In the course of these studies (12) it was shown, that the syndrome may develop in conjunction with certain infectious diseases (streptococcal infections, salmonellosis, mononucleosis, primary atypical pneumonia, hepatitis epidemica, vaccinia and adenoviral infections) without administration of drugs. But it may also be caused exclusively by drugs (barbiturates, antiepileptics, mercury, sulphonamide, acetylsalicylic acid, codeine, meprobamate, butazolidine). Alimentary causes are also probable in some cases. Pathogenesis will be dealt with, in detail in a future paper.

Since the syndrome may be caused both by infection and by drugs, a combination of the two should provide a very favourable soil for it. In order to be able to assess the rôle of the drug under these circumstances, a test would be desirable. It was therefore decided to try the thrombocyte test. In allergic manifestations, thrombocytes quite often diminish in the peripheral blood. In an attack provoked by probenecid-penicillin the number of thrombocytes fell to 20,000. A total of 47 patients were examined in the acute stage: three had less than 50,000 thrombocytes, ten between 50,000 and 100,000, eight 101,000–150,000, and nine 151,000–200,000. The subsequent rise was pronounced in all cases except three. The mean value in the first test was thus 146,000 and in the second 295,000.

TEST

A dose of the suspected drug was given on an empty stomach. The quantity was usually the same as the patient had had previously, sometimes half the previous dose. The thrombocyte count was taken before administering the drug and thereafter each half-hour for two hours. A lowering of the count by at least 20 per cent was regarded as a positive reaction.

MATERIAL

The tests were made on 29 patients with febrile mucocutaneous syndrome. Twenty-seven of them had an acute infection, the remaining two showed no such symptom. The test was not made until the syndrome had been absent for at least some days. Two other cases of febrile allergic exanthema have been included in which the outcome of the test was of special interest for the subject of the study.

RESULTS

The patient often developed a *clinical reaction* in the form of erythema or exanthema, sometimes of conjunctivitis, enanthema and even fever. Usually this clinical response did not come so quickly as to be apparent during the thrombocyte test, but later in the day or on the next day. The results are shown in table 1, which lists the 19 of the 29 cases which responded positively to the provocation, as well as the two additional cases of allergic exanthema.

A comparison of the results for the cases of febrile mucocutaneous syndrome shows the following:

Clinical reaction and positive thrombocyte test	5
Clinical reaction	11
Positive thrombocyte test	3
Negative	10
Total.....	29

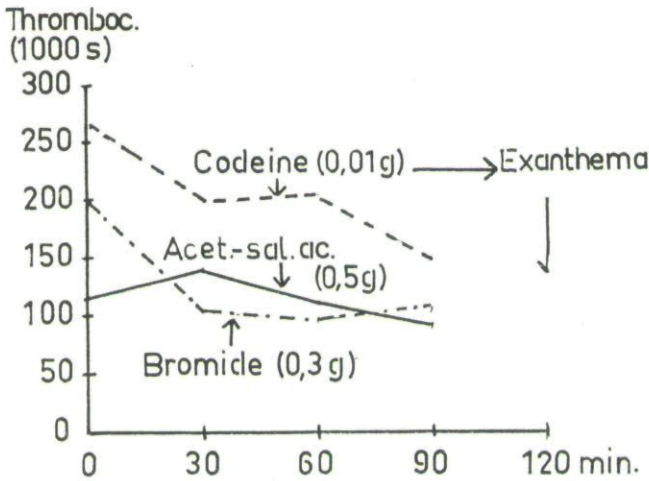


Fig. 1.

Case 2. Thrombocyte test and clinical reaction after acetylsalicylic acid, codeine and bromide.

Of the skin reactions three were erythema, two being generalized and fairly severe with pronounced itch (case records 4, 8), and one more local (case record 1). The exanthemas consisted of more or less diffuse maculopapulous efflorescences. Conjunctivitis occurred in six cases, enanthema in two, and rise of temperature in nine. The onset of the clinical reaction came at the earliest after 1 hour and at the latest after 27 hours (mean 7 hours), the rash lasting from a few hours to four days. In some cases the duration has not been specified.

The situation is often complicated by the fact that the patient has been given several drugs or a mixed drug. Thus an exact investigation requires testing not merely of each drug but also of their ingredients. Single drugs or ingredients which this study has shown can provoke reactions with skin symptoms are acetylsalicylic acid (cases 1, 3), codeine (case 2), probenecid (cases 7, 9, 11, 13), Salazopyrin (case 8), sulphamethoxypyridazine (cases 16, 17, 19) and quinine sulphate (case 10).

In case 2 the patient had taken magnecyl codeine (acetylsalicylic acid codeine), and also bromide. The thrombocyte

TABLE I

Diagnosis of basic disease	Drug	Thrombocyte test (% decrease)	Clinical reaction			
			Skin	Mucosa	Fever	Onset after hrs
						Dur.
<i>Provocation test in syndrome mucocutaneum febrile.</i>						
1. Streptoc. tonsill.	Acet. sal. ac.	16	Eryth.	-	-	8 ?
2. Toothache (No infection)	Acet. sal. ac.	29	-	-	-	-
	Codeine	51	Exanth.	-	-	2 5 h
	Bromide	40	-	-	-	-
	Acet. sal. ac.	45	-	-	-	-
3. Upper resp. inf.	Sulfadital 1)	21	Eryth.	Conj.	37°·8	1 3 h
4. Pneumoc. mening.	Sulfadon 2)	17	Exanth.	Conj.	-	2 1 d
5. Infect. mononuel.	Phenacetin	0	-	-	-	-
	Coffeine	0	-	-	-	-
	Propyphenazone	0	-	-	-	-
	Persedon (Roche)	35	-	-	-	-
	Saridon	9	Exanth.	-	-	2 ?
6. Pneumoc. tonsill.	Penic. G	20	-	-	-	-
	Probenecid	6	Exanth.	Conj.	39°·3	8 2 d
	Salazopyrin 3)	0	Eryth.	-	37°·7	27 1 d
7. Infect. mononuel.	Probecellin					
8. Chronic arthralgia (No infection)	Probecellin	18	-	-	-	-
	Probenecid	19	Exanth.	-	-	12 2 d
	Coffeine	2	-	-	-	-
	Camphor	6	-	-	-	-
10. Streptoc. pharyng.	Phenacetin	10	-	-	-	-
	Quinine sulph.	25	Exanth.	-	-	8 1 d
	Sulfdurazin 5)	0	-	-	-	-

11. Streptoc. tonsill.	Probecellin	{ Penic. G Probenecid	0	-	-	-	-
12. Fever of unknown origin	Triocillin 4)		29	Exanth.	Conj.	10	?
13. Infect. mononucle.	Probecellin	{ Penic. G Probenecid	15	-	-	39°.1	5
14. Acute sinobronch.	Sulfadital 1)		11	Exanth.	-	37°.8	8
15. Streptoc. tonsill.	Probecellin	{ Penic. G Probenecid	18	Exanth.	-	39°.9	12
16. Prim. atyp. pneum.	Sulfdurazin 5)		14	-	-	-	-
17. Streptoc. otitis	Lederkyn 5)		22	-	-	-	-
18. Prim. atyp. pneum.	Calciopen 6)		11	Exanth.	-	38°	1 1/2
	Acet. sal. ac. + cod.		0	Exanth.	Conj.	38°.5	4
19. Adenovirus inf.	Pertin (Astra)		10	-	-	-	-
	Sulfdurazin 5)		14	Exanth.	Conj.	39°.6	3
					Enanth.		4
<i>Provocation test in allergic exanthema.</i>							
20. Infect mononucle. + eryth. nodosum	Acet. sal. ac.		13	-	-	-	-
	Codeine		21	-	-	-	-
21. Acute sinuit. + Allergic exanth.	Acet. sal. ac. + cod.		7	Urticaria	-	-	3
	Meropenin 7)		0	Exanth.	Conj.	-	2 1/2
	Meropenin (5 days later)		70				several days

1) Sulphonazole + sulphadiazine + sulphamerazine.

2) Sulphamerazine + sulphaproxyline.

3) Salazo — sulphapyridine.

4) Phenoxymethylpenicillinpotassium + sulphadiazine + sulphamerazine + sulphadimidine.

5) Sulphamethoxypyridazine.

6) Phenoxymethylpenicillin calcium (penicillin V calcium).

7) Phenoxymethylpenicillin (penicillin V).

test was positive for all three ingredients, but remarkably enough the most marked reaction came after codeine, when exanthema as well appeared (Fig. 1). In this context the patient with erythema nodosum (case 20) is of interest. This patient, too, had taken magnecyl codeine. The thrombocyte test was positive for codeine, but not for acetylsalicylic acid + codeine. The combination, on the other hand, produced a clinical response with urticaria on shoulders, chest and back. Case 10, in addition to Sulfdurazin, had had a drug consisting of four ingredients, but a reaction appeared in response to quinine sulphate alone. The patient who had had Saridon (case 6) reacted clinically to the mixed drug, but in the thrombocyte test only to one ingredient (Persedon).

The drug probecillin consists of benzyl penicillin G and probenecid, which delays the excretion of penicillin, thereby raising its level in the blood and prolonging its activity. Both penicillin and probenecid have allergenic potency. In prophylactic trials by *Berry & Farber* (3) against streptococcal infections, penicillin produced skin reactions in 90 of 33,827 persons (0.27 %). *Boger & Strickland* (4), in a review of the literature, found skin eruptions from probenecid in 30 of 2,502 cases (1.35 %).

In the tests concerning probenecid-penicillin allergy (11), referred to above, Probecillin (penicillin G + probenecid) gave delayed reactions in a very high percentage of streptococcal infections (20 % in scarlatina, 8 % in other streptococcal diseases). On the other hand penicillin G alone produced no reaction.

If we now look at the five patients treated with Probecillin, only one reacted positively to penicillin G in the thrombocyte test. The same patient had a pronounced clinical reaction after probenecid (case 7, fig. 2). In one case, furthermore, probenecid produced positive reactions both in the thrombocyte test and clinically (case 11), in three cases clinically alone (7, 9, 13), and in the fifth in the thromocyte test alone (15).

Manifestly probenecid has the strongest allergenic effect. But penicillin, too, may be of significance. In my comparative

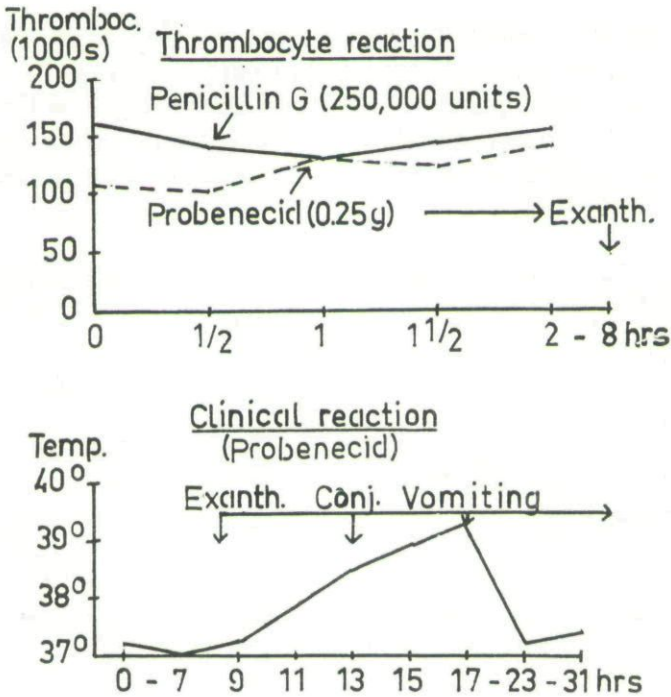


Fig. 2.

Thrombocyte reaction after penicillin G and probenecid. Clinical reaction caused by probenecid.

test Vebecillin (penicillin V + probenecid) gave rise to a still higher percentage of reactions (scarlatina 45 %, other streptococcal diseases 22 %) than Probecillin (11). The difference was statistically significant. Whether this is due to higher concentration of penicillin in the blood or to the type of penicillin is unknown.

Case 21 is of interest as example of the provocative effect of penicillin V (fig. 3). A 4-year-old boy with sinusitis developed serious swelling on the back of the hands, maculae on the back and petechiae on the trunk on the third day of treatment with penicillin V. The treatment was discontinued. A thrombocyte test after disappearance of the symptoms was entirely negative, but exanthema appeared on the neck after

3 hours. Treatment was reinstituted for four days, during which the exanthema became increasingly widespread on face and trunk, accompanied also by conjunctivitis. After the last dose of the drug a new thrombocyte test was highly positive (70 %).—In case 18 penicillin V calcium yielded a positive thrombocyte test.

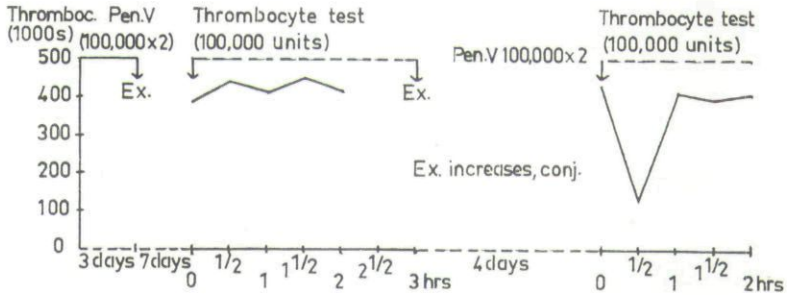


Fig. 3.

Case 21. Allergic syndrome caused by penicillin V and the thrombocyte reaction at the beginning and end of the test.

Thus both penicillin and probenecid have an allergenic effect, though the latter is most active. They presumably potentiate one another, since the combined drug produces a great increase in reactions, compared with the two drugs individually. The high incidence of allergic reactions in my trials in streptococcal infections, on the other hand, was manifestly occasioned also by the nature of the disease (the highest incidence occurred with scarlatina).

It has been found that sulpha drugs may cause the syndrome. A sulpha compound had been taken by a person without acute infection—who „thought it was a vitamin“—with resulting development of symptoms. In the present material one case (8) occurred after Salazopyrin, three (cases 16, 17, 19) after sulphamethoxypyridazine, and three (cases 4, 5, 14) after combined drugs, all with positive clinical response to provocation. Only one patient (case 4) had a positive thrombocyte test as well.

It is evident that, when reactions may be caused both by penicillin and by sulpha, a drug such as Triocillin which contains them both can give rise to allergic syndromes (case 12).

Ten patients reacted negatively to provocation. In a patient with mononucleosis in which the syndrome appeared after treatment with Probecillin for seven days, the thrombocyte test showed a decrease of only 9 per cent after penicillin G and combined drugs and was entirely negative after probenecid. Especially remarkable, however, is that no less than four patients had primary atypical pneumonia, in one case treated with sulpha - Gantrisin - (2 days), one Sulfadon (3 days) + DBED penicillin (1 injection), one Probecillin (2 days) + acetylsalicylic acid, and one acetylsalicylic acid + diemalphenacetin (6 days). Tests with all drugs were negative. There is reason to suppose that the nature of the disease was the decisive factor. Moreover the drugs had been given for a fairly short period, so that there was probably no time for sensitization to develop. The same may be said of the remaining cases, with the exception of one in whom the syndrome was probably caused by butazolidine after 5 months of treatment.

The drug may nevertheless be of significance without its effect becoming apparent through provocation tests. The dose may be too small or the second component—the underlying infection with its antigen-antibody reaction—may have disappeared. One knows, too, that after certain drugs, such as antiepileptics and Salvarsan, the antigenic potency often expires after the allergic reaction has broken out. This has been seen in certain cases of probenecid-penicillin allergy.

The clinical reactions were twice as numerous as the reactions to the thrombocyte test (16 patients against 8). The thrombocyte test in isolation was positive in three patients, the clinical test in eleven. Even if it has been found that the thrombocytes often diminish in number in the mucocutaneous syndrome, the reaction is not absolute and is generally fairly slight (see above). It is, moreover, quite natural that the provocation chiefly affects the skin and mucosa. These are obviously the organs which react to these allergens. The

thrombocyte reaction may perhaps be an indication of a more advanced stage of the allergic syndrome. This is illustrated by case 21 (fig. 3). The thrombocyte reaction was positive only after the patient had been treated for some days.

The results of all tests made in the 21 positive cases are compared. Altogether 41 tests were made, the 31 positive reactions being shown in table 2. The + and — signs for each individual test are placed in corresponding positions in the columns for thrombocyte and clinical reactions.

TABLE 2

Drug	Thrombocyte reaction	Clinical reaction
Acet. sal. ac.	— + +	+ — —
Codeine	+ +	+ —
Acet. sal. ac. + codeine	—	+
Persedon	+	—
Saridon	—	+
Bromide	+	—
Quinine sulphate	+	+
Sulpha: Salazo-sulphapyridine	—	+
Comb. drugs	+ — —	+ + +
Sulphamethoxypyridazine	— — —	+ + +
Probecillin: Penicillin G	+ — — — —	— — — — —
Probenecid	— — + — +	+ + + + —
Penicillin V	+ +	+ —
Triocillin (pen. V + Comb. sulpha drugs)	—	+
Total.....	13 + 17 —	18 + 12 —

It is seen that there were 13 positive thrombocyte reactions against 18 clinical. The incidence of reactions to analgetics was roughly the same in both tests, whereas sulpha produced a positive clinical response in all seven cases, though only one of them was positive also in the thrombocyte test. The majority of positive reactions are clinical too with probenecid. Comparing sulpha and penicillin, one finds that the latter must have a considerably lower allergenic potency. As regards penicillin, it is the combination with probenecid that has been the most decisive factor in the allergic reaction.

DISCUSSION

Syndroma mucocutaneum febrile, which covers a number of conditions often described previously as separate diseases or syndromes, is an allergic reaction. This has been shown by the author earlier and is further supported by the present study. The syndrome may appear in response to certain diseases and to certain drugs. The „right“ combination of disease and drug should afford particularly favourable conditions for the syndrome to manifest itself. The rôle of the drug under such circumstances is illustrated by this study of the reactions to provocation. The thrombocyte test showed fewer positive results than the number of clinical reactions. Nineteen of twenty-nine examined patients reacted positively: to the thrombocyte test in three cases, clinically in no less than eleven, and by both forms of reaction in five. The explanation is principally that the skin and mucosa are the organs mainly affected in this syndrome.

The diseases from which the patients were suffering consisted in five cases of haemolytic streptococcal infections, in two of pneumococcal. Four patients had infectious mononucleosis, two primary atypical pneumonia, and one an adenoviral infection. The aetiology in three cases could not be established, and two patients were without infection.

Of the various drugs used for treatment, positive reactions were obtained to acetylsalicylic acid and codeine, alone or in combination, bromide, quinine sulphate (ingredient in one agent), and the complex drug Saridon. Sulphonamides, in one case in the form of Salazopyrin, in three in the form of combined drug, and in three as the longacting sulphametoxypridazine, likewise produced positive reactions. Penicillin G and V as well had allergenic action, though far weaker than the sulphonamides. The combination of penicillin and probenecid makes for extremely high allergenic potency, as pointed out by the author previously and confirmed by the present trials, probenecid being the most active agent from the provocation aspect. As might be expected, positive reactions were also obtained with combinations of penicillin and sulpha.

In the majority of the cases the basic disease (streptococcal infection, mononucleosis, primary atypical pneumonia) may itself produce the syndrome, as the author has found in a larger clinical series, but the provocative rôle of the drug is clearly documented by the outcome of the tests. In fifteen of the cases the drugs had been administered during so long a period (4 days to 2 weeks) that a delayed reaction was likely.

In the ten negative cases—one streptococcal and one pneumococcal infection, four primary atypical pneumonia, one mononucleosis, one rheumatoid arthritis, two infections of unknown aetiology—the disease was probably of more decisive importance. In eight of them the drugs had been given during a fairly short period, so that there was less likelihood of sensitization.

SUMMARY

The rôle of drugs as the cause of *syndroma mucocutaneum febrile* is illustrated by provocation reactions. In nineteen of twenty-nine patients, trials with suspected drugs produced positive reactions clinically or using the thrombocyte test. Clinical responses were more frequent than positive thrombocyte reactions, probably because the skin and mucosa are the organs principally concerned in the syndrome. The reaction appeared in response to acetylsalicylic acid, codeine, bromide, quinine sulphate, Saridon, Salazopyrin, combinations of sulpha, and sulphamethoxypyridazine. Penicillin G and V also produced some reaction, especially in combination with probenecid. The combination with sulpha may have the same result. The underlying infection was in most cases of a kind such as to induce the syndrome, but the provocative rôle of the drugs was documented by these trials. In the ten cases with negative provocation tests the disease was probably of more decisive importance.

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