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DRUG ERUPTIONS

*A series of 464 cases in the Department of Dermatology,
University of Turku, Finland, during 1966-1970*

By

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Drug reactions due to innumerable new drugs form an increasing factor of complication in modern therapy. Drug eruptions of different types and degrees are the most common manifestations of drug reaction. Haematological complications, gastrointestinal disturbances, fever, vasculitis, lymphadenopathy, neurological manifestations, pulmonary infiltration as well as hepatic- and renal injuries are other types of reactions (12, 35).

Drug reactions are either allergic or toxic by nature. The concept of drug allergy is very complicated, as there is no pathognomonic symptomatology or specific pathology or any simple and reliable test with which this type of allergy can be detected (13, 36).

Determination of agglutinins, precipitins and other serum antibodies, basophil- and mast cell reactions, thrombocyte reactions, lymphocyte-transformation test and radioallergo-absorbent test have been developed to assist intracutaneous and provocation tests (18, 27, 30, 31, 33), but these methods cannot be adapted to routine use due to their demanding technical performance. The clinical picture is still the most important diagnostic criterium in drug eruptions. The eruption can vary between mild pruritus and severe, even fatal reactions. Drug eruptions can resemble almost any other known skin disease morphologically, but as almost any drug can cause

different types of reactions, the drug cannot be named solely on basis of the clinical picture (35).

The most common skin manifestations are exanthematous eruptions, urticaria, erythema multiforme, erythema fixum, and purpura. The most severe types are exfoliative dermatitis and bullous drug reactions: Stevens-Johnson's syndrome and Lyell's syndrome, i. e. toxic epidermal necrolysis. Erythema nodosum, lichen planus, acne, and vegetating or tumorous lesions are seldom seen (12, 33, 35). A combination of the different types is, however, often seen.

Literature dealing with drug reactions is very wide and varied (6, 7, 11, 12, 28, 33, 35). The drug eruptions treated in the Department of Dermatology, University of Turku during 1966-1970 will be presented in the following.

MATERIAL AND RESULTS

During 1966-1970 464 cases, 135 males and 329 females, suffering from drug eruptions, were treated in the Department of Dermatology, University of Turku. The mean age of the patients was 42 years, the youngest patient being one, the oldest 85 years. The yearly distribution of the patients during 1966-1970 was as follows:

Cases	1966	1967	1968	1969	1970	Total
Male	25	30	21	24	35	135
Female	46	61	52	82	88	329
Total	71	91	73	106	123	464

287 patients were treated as in patients and 177 as out patients. 68 patients (14 %) were emergency cases. The mean time of the treatment was 11 days. 98 patients (21 %) had suffered from drug eruption earlier. Sixteen out of these had had eruptions due to two or three different drugs. The present eruption was due to the same drug as before in 41

patients (9 %). In these cases the patient had often forgotten his drug allergy, or taken the drug by mistake instead of some other substance.

It could be suspected in 322 cases that the causative agent of the present eruption was only one drug. In 132 cases the patient had received two or more drugs that could have caused the skin reaction. The diagnosis was confirmed in some patients on the basis of a previous allergy. Provocation or scratch tests were carried out in 102 patients.

Two patients died. One had Lyell's syndrome associated with long acting sulphonamides, and the other Stevens-Johnson's syndrome due to phenylbutazone. The direct cause of death of the latter was perforation of a duodenal ulcer.

The cutaneous manifestations of drug reactions

The distribution according to the morphological type of eruption in the whole material is presented in Table I. There were 214 cases of exanthema. This manifestation occurred in association with almost every drug, but most frequently in association with sulphonamides (117 cases), ampicillin (26 cases), tetracycline (7 cases) and other antibiotics and chemotherapeutics, not including penicillin, which most frequently caused urticaria.

The total number of urticaria cases was 107. In addition to penicillin, sulphonamides, other antibiotics, some analgetics, and barbiturates, urticaria was relatively often caused by iodine and Vitamin B. Seven anaphylactic reactions were caused by penicillin (4 cases), chloramphenicol, iodine, and an analgetic (one case each).

The largest group by three was formed by erythema fixum, of which there were 46 cases altogether. 31 were caused by analgetics, antipyretics and antirheumatics. Barbiturates, meprobamate and iodine were other causative agents. Ampicillin and nitrofurantoin were rare causes of erythema fixum (one case of each).

TABLE 1
Drug Eruptions in 464 Patients According to the Causative Agents and Morphological Types of Reaction.

	Urticaria and/or angioneurotic oedema	Exanthema	Exfoliative dermatitis	Anaphylactic reaction	Erythema multiforme	Stevens-Johnson syndrome	Lyell's syndrome	Erythema fixum	Purpura	Photosensitivity	Other	Total
Sulphonamides	27	117	3	—	14	12	5	1	1	9	—	187
Penicillin	24	8	1	4	1	—	—	—	—	—	—	35
Ampicillin	3	26	—	—	2	1	—	1	—	—	—	33
Tetracycline	3	7	—	—	—	—	—	—	—	—	—	10
Chloramphenicol	3	1	—	1	—	—	1	—	—	—	—	6
Streptomycin	3	2	—	—	—	1	—	—	—	—	—	6
Nitrofurantoin	1	2	—	—	—	—	—	1	—	—	Fever 1	5
Nalidixic acid	—	1	—	—	—	—	—	—	—	—	—	1
Trimethoprim	—	2	—	—	—	—	—	—	—	—	—	2
PAS	—	—	—	—	—	—	—	—	—	2	—	2
Etambutol	—	1	—	—	—	—	—	—	—	—	—	1
Ethionamide	—	1	—	—	—	—	—	—	—	—	—	1
Acetylsalicylic acid	6	2	—	—	1	—	—	9	—	—	—	18
Salicylamide	2	1	—	—	—	—	—	—	—	—	—	3
Phenazonesalicylate	3	2	—	—	—	—	—	2	—	—	—	7
Phenacetin	2	—	—	—	—	—	—	2	—	—	—	4
Aminophenazone	1	—	—	—	1	2	—	—	—	—	—	4
Phenylbutazone	—	—	—	—	1	1	—	4	1	—	—	7
Oxyphenylbutazone	—	2	—	—	2	—	—	1	—	—	—	5
Chlormezanone	—	1	—	—	1	—	—	1	—	—	—	3
Coumestrol	2	2	—	—	—	—	—	1	—	—	—	5

TABLE
Types of Eruptions According to the

Quality of sulphonamide		Exanthema	Exfoliative dermatitis
Long-acting	S-methoxydiazine	10	-
	S-methoxypyridazine	14	-
	S-dimethoxin	2	-
	S-phenazol	-	-
	S-methoxazol	4	1
Combination-preparations	S-methoxypyridazine + S-methizol	53	-
	S-proxylin + S-merazin	-	-
	S-tolamid + S-merazin	2	-
	S-methoxydiazin + S-furazol	1	-
	S-diazin + S-merazin + S-dimidin	4	-
	S-diazin + S-merazin + S-methazin	-	1
	S-methazin + S-acetamide	12	-
Short-acting	S-methizol	1	-
	S-diazin	2	-
	S-dimidin	2	-
	S-furazol	2	-
Others	Salazosulphapyridin	2	-
	„Sulfa“	3	1
Locally administered	S-thiazol, S-acetamide, para-aminobenzolsulphonbenzylamide	1	-
sulphonamides	S-methizol	2	-
amides	Sulphonilamide	-	-
Total		117	3

There were 25 cases of erythema multiforme, more than half of which (14 cases) were caused by sulphonamides. Similarly, 12 out of 19 Stevens-Johnson syndromes were due to sulphonamides. Aminophenazone (2 cases), ampicillin, streptomycin, phenylbutazone, chloroquin, and a combination of analgetics (one case of each) were other causes. Six cases

Quality of Sulphonamide in 187 Cases.

Urticaria and/or angioneur. oedema	Erythema multiforme	Stevens- Johnson's syndrome	Lyell's syndrome	Photo- sensitivity	Total
4	2	2	—	1	19
3	3	1	2	—	23
—	—	—	—	1	3
1	—	—	—	—	1
1	—	—	—	1	7
14	4	4	3	2	80
—	1	—	—	—	1
1	1	—	—	—	4
—	—	—	—	—	1
—	—	1	—	—	5
—	—	—	—	—	1
—	1	2	—	1	10
—	—	—	—	—	1
—	—	—	—	—	2
—	—	—	—	—	2
—	—	—	—	1	3
—	—	1	—	—	3
2	2	1	—	1	10
—	—	—	—	—	—
1	—	—	—	—	2
—	—	—	—	—	2
—	—	—	—	1	1
27	14	12	5	9	187

of Lyell's syndrome, i. e. toxic epidermal necrolysis, were observed, of which five were due to sulphonamides and one to chloramphenicol.

Seventeen cases of exfoliative dermatitis were observed. This reaction was typical of gold (4 cases) and carbamazepin (5 cases). Erythrodermia was also noted in association with

TABLE
The Five Cases of Lyell's Syndrome

Case No.	Sex	Age	Previous drug allergy	Indication of the treatment	The quality and doses of sulphonamides
1	F	45	None	Urinary tract infection	S-methoxypyridazine 250 mg $\times$ 3 + S-methizol 250 mg $\times$ 1
2	F	40	Penicillin	Urinary tract infection	S-methoxypyridazine 500 mg $\times$ 2 for 7 die after which 500 mg $\times$ 1
3	F	54	None	Urinary tract infection	S-methoxypyridazine 250 mg $\times$ 3 + S-methizol 250 mg $\times$ 3
4	M	64	None	Tonsillitis	S-methoxypyridazine 50 mg $\times$ 2
5	F	12	Penicillin	Urinary tract infection	S-methoxypyridazine 250 mg $\times$ 3 + S-methizol 250 mg $\times$ 3

sulphonamides, penicillin, chlorpromazin, phenemal and phenytoine.

The material contained 13 cases of photosensitivity. The causative agents were sulphonamides (9 cases), para-amino-salicylic acid (2 cases) and chlorpromazine (2 cases). Seven cases of purpura were observed due to meproamate, phenemal, sendoxane, phenylbutazone and some analgetic preparations. Further, 2 cases of vasculitis similar to erythema nodosum were caused by analgetics and one fever reaction by nitrofurantoin.

Reactions caused by the individual drugs

From Table 1 can be seen that 52 drugs caused skin reactions. "Analgetic" drugs were regarded as a separate group of preparations composed of several different drugs. Provocation tests with the single components of these drugs were not carried out separately. Uncertain and complicated cases in which the

Caused by Sulphonamides.

Manifestation of the symptoms since the institution of treatment/days	Progress and complications of the disease
21	Severe bullous eruption followed by sepsis, hematemesis and exitus
10	Appeared as bullous exanthema. Nails loosened. Residual pigmentation and scars
10	Initiated as bullous exanthema with epidermolysis
17	Manifested in the beginning as Stevens-Johnson's syndrome. Embolia art. carot. interna. Recovered from embolectomy.
20	Initiated as Stevens-Johnson's syndrome. Residual pigmentation. Conjunctival synecchia operated later on.

drug etiology was not confirmed, were excluded from the material. Skin reactions due to locally used drugs were also excluded, except as to five systemic reactions caused by locally used sulphonamides. A more detailed discussion of the types of eruption due to different drugs is presented in the following and in addition to this, attention is paid to previous drug allergies, duration of the drug therapy prior to the eruption, and to the provocation tests.

1. Antibiotics and chemotherapeutics

Sulphonamides

Skin reactions due to sulphonamides occurred in 187 cases, i.e. one third of the whole material. The yearly frequency was 28 cases in 1966, 35 cases in 1967, 26 cases in 1968, 47 cases in 1969 and 51 cases in 1970. Nineteen patients had previously suffered from drug reaction caused by sulphonamides, and 20 patients had had other drug reactions.

In 124 patients the indication for treatment was urinary tract infection. In 61 patients the skin symptoms appeared 1 to 7 days after institution of the treatment, and in 126 patients after more than 7 days.

As it can be seen in Tables I and II, the most common type of eruption was exanthema, which was found in 117 patients. It was mostly wide-spread, consisting of large macules with a purplish shade and was often associated with swelling in the face, palms, and soles. Exfoliative dermatitis developed in three patients. Urticaria and/or angioneurotic oedema was noted in 27 cases. Erythema multiforme was seen in 14 patients, of which three presented partly bullous and haemorrhagic cutaneous changes.

There were 12 cases of Stevens-Johnson's syndrome with more severe symptoms. The eruption was bullous, the mucous membranes affected, and fever and nausea were present as systemic symptoms. Toxic epidermal necrolysis, i.e. Lyell's syndrome, developed in five patients that are being dealt with more closely in Table III.

In three patients (Cases 1, 2 and 3) the eruption started as exanthema that rapidly took a vesicular form with large, blisters, the skin loosened in sheets from large surfaces and the mucous membranes were affected. The clinical picture of Case 1 was septic with severe symptoms. Exitus followed after 8 days' hospital treatment. The clinical picture of two patients (Case 4 and 5) was in the beginning similar to Stevens-Johnson's syndrome, but changed into epidermolysis.

Nine patients had photosensitivity due to sulphonamides. Furthermore photosensitivity occurred as a later manifestation in six patients that had first had an exanthematous reaction.

From Table II it appears that 53 patients had received long-acting sulphonamides. 23 of them had received sulphamethoxypyridazine and 19 sulphamethoxydiazine. Combinations of different sulphonamides had been administered to 108 patients. 80 of which had received the combination of sulphamethoxypyridazine and sulphamethizole. The yearly increase of the drug reactions due to these combined preparations in Finland was as follows: 5 cases in 1966, 7 cases in 1967, 11 cases in 1968, 26 cases in 1969 and 31 cases in 1970.

The combination of sulphamethoxazole and trimethoprim had been given to 8 patients altogether in 1970, when this combination was introduced in Finland. Trimethoprim was the causative agent in 2 cases and sulphamethoxazole in 6 cases. Short-acting sulphonamides had been given to 8 patients and salazosulphapyridine to 3 patients. Any knowledge of the quality of the sulphonamide given to 10 patients was not obtained. The reaction was caused by locally administered sulphonamide in five patients (powder and ointment).

In Table II the type of sulphonamide and the skin reaction caused by it can be compared. Thus it can be seen that more severe skin reactions were more frequent in patients who had received long-acting sulphonamide. All patients suffering from Lyell's syndrome (Table III) had been given sulphamethoxypyridazine either as such or combined with sulphamethizole.

One out of 12 cases of Stevens-Johnson's syndrome had had long-acting sulphonamides, and 7 patients had been treated with different sulphonamide combinations.

Peroral provocation tests were usually carried out 1-2 months after the eruption. The patients received the same sulphonamide preparation as before and the dose was the same or half of the dose normally used—e.g. 250 or 500 mg sulphamethoxypyridazine in one dose. The patient was then observed in hospital at least two days.

Provocation tests with sulphonamides were carried out in 17 patients and were positive in 14 cases. Patients with Stevens-Johnson's syndrome and Lyell's syndrome were not tested.

In addition to this, penicillin scratch test was carried out in 8 patients. The test was positive in one patient, who had earlier had urticaria due to penicillin. Further, provocation tests that proved negative were carried out with the following drugs: ampicillin (2 cases), tetracyclin (2 cases), nalidixic acid (2 cases), and with the following one case each: oxyphenbutazone, tolbutamide, chlorthiazide, thiamazole, and lynestrenole.

Penicillin

Eruptions due to penicillin were registered in 35 cases. Their annual number remained almost the same throughout 1966-1970: 7 cases in 1966, 5 cases in 1967, 7 cases in 1968, 6 cases in 1969 and 10 cases in 1970.

Three patients had had penicillin-eruptions earlier. One of these patients had forgotten his allergy, one took a tablet of penicillin by mistake instead of aspirin, and one received a combination of sulphonamide and penicillin, not being aware of the penicillin.

Urticaria and/or angioneurotic oedema occurred in 24 patients i.e. two thirds of the cases. In two patients urticaria was associated with a very severe oedema and erythema. There were 5 cases of exanthema. Two of them were associated with lymphadenopathy. One patient had stomatitis and purpura in the legs in addition to exanthema. Four patients developed an anaphylactic shock. One patient had erythema exudativum multiforme, and exfoliative dermatitis developed in one patient.

Symptoms of anaphylactic shock appeared in 1 minute in a patient who had been given penicillin as an intramuscular injection and in 15 minutes to 2 hours in three other patients who had been given tablets. In less than 6 hours other types of reaction were seen in 5 patients, and in 1 to 5 days in 9 patients. In 7 patients the symptoms did not appear until 7 to 10 days after start of the treatment, or after a latency period of 7 to 10 days from the completion of the treatment. Later on, a scratch test with benzylpenicillin sodium of 10,000 IU/ml was carried out in 8 patients, of which 5 had had urticaria or angioneurotic oedema, 2 exanthema, and one patient an anaphylactic reaction. Only 3 cases were positive, of which two were urticaria cases. The third patient was a hospital maid, who had an anaphylactic shock due to a penicillin tablet. Later on she was affected with a severe angioneurotic oedema after having wiped crumbs of a penicillin tablet from the shelf of a medicine cupboard.

To exclude other simultaneously given drugs a peroral provocation test with nicotinic acid was carried out in one patient, and a combination of sulphamerazine, sulphadiazine, and sulphamethazine in another. Both tests were negative.

Ampicillin

Thirty three skin reactions were regarded as due to ampicillin. The number of them increased during the years 1966—1970 as follows: in 1966 one case, 2 cases in 1967, 5 cases in 1968, 8 cases in 1969 and 17 cases in 1970. Two patients had earlier had drug eruption from penicillin, and one from streptomycin. Six patients were allergic to sulphonamides. Two patients had been administered ampicillin for the treatment of infectious mononucleosis and others for different infectious diseases.

Exanthematous eruptions occurred in 26 patients, both patients with mononucleosis included. Purpura occurred in 12 patients in association with exanthema and stomatitis in two. The palms and soles were swollen and in two of them blistered, too.

There were 3 cases of urticaria and angioneurotic oedema. One of them was associated with vasculites in the legs resembling erythema nodosum. Erythema multiforme was indicated in two patients and Stevens-Johnson's syndrome with severe bullous mucocutaneous symptoms developed in one. This patient had had exanthema due to penicillin two years earlier. One patient had a fixed, partly bullous eruption on the skin of the extremities.

The skin symptoms appeared usually after drug therapy for several days: 7–16 days in 23 cases. Four patients had high fever during 2–6 days before the onset of the eruption—the treatment continued till the eruption became manifest. The symptoms appeared after 3–6 days in 9 patients and in one day only in one patient with previous penicillin allergy.

Scratch-test with penicillin was carried out in 5 cases. Only one was positive. This was a patient with chronic bronchitis who had previously had an eruption due to sulphonamide. Only one peroral ampicillin provocation was carried out. One patient with a negative scratch-test was given 250 mg ampicillin per os, which led to the manifestation of exanthema in 6 hours.

One of the two patients with mononucleosis had a negative penicillin scratch-test; in the other it was not carried out. The latter patient was given another ampicillin treatment by accident one month after the previous scheme with the result that exanthema recurred.

In addition to this, provocations with different analgetics were carried out in two patients, and sulphamethoxypyridazine was tested in one. The tests were negative.

Tetracycline

An eruption due to tetracycline was indicated in ten patients. Five of them had been affected with drug allergies before. Two had suffered from an eruption due to both sulphonamide and penicillin. It can be seen from Table I that exanthematous eruption occurred in 7 patients. Vasculites in the legs similar to erythema nodosum were associated with exanthema in one patient. Three patients had urticaria and/or angioneurotic oedema. The skin symptoms occurred after 1-3 days in 8 cases, and in 2 cases after treatment for 2 weeks. Provocation-test with 250 mg tetracycline per os was carried out in two patients with urticaria. One of them had received chloramphenicol in addition to tetracycline. Tetracycline caused urticaria in the test; chloramphenicol was negative. The other patient had been given a combination of sulphonamide and penicillin prior to tetracycline treatment. The latter caused urticaria in the provocation. Penicillin scratch-test was negative as well as the peroral provocations with sulphonamide and penicillin.

Chloramphenicol

Chloramphenicol caused skin reactions in 6 patients that have been more closely discussed in Table IV. Three of them had had drug allergies before. Urticaria and/or angioneurotic oedema occurred in 4 patients. Case 1 had been affected earlier with urticaria due to chloramphenicol. Now, 2 hours after having given chloramphenicol syrup to her baby, thereby spilling it on her hands, her face and hands became swollen. Case 4 developed an anaphylactic reaction 3 hours after 500 mg chloramphenicol. The reaction recurred in the provocation test.

Lyell's syndrome developed in Case 6. This patient was a female of 76 years and received a dose of 250 mg $\times$ 4 chloramphenicol for 6 days for the treatment of bronchitis. Fever set on after withdrawal of the treatment, and in 2 days a vesicular eruption appeared that rapidly changed into epidermolysis. With steroid therapy the patient recovered. Hospital treatment lasted for 20 days. A dose of 100 mg chloramphenicol caused exanthema in a provocation test later on.

Streptomycin

Six patients had skin reactions due to streptomycin. Urticaria and/or angioneurotic oedema occurred in 4 patients. The injection sites were swollen in one of them and the palms and soles in another. In 4 the skin reaction manifested after 9-16 days of treatment, in two of these after a latent period of 7-9 days with the clinical picture of serum sickness. In addition, there was one case of exanthema after 4 days of treatment and one case of Stevens-Johnson's syndrome, the first symptoms of which broke out already after 3 days.

TABLE
Drug Eruptions due

Case No.	Sex	Age	Previous drug allergy	Indication of the treatment	Dose
1	F	29	Chloramphenicol	The patient gave Chl. syrup to her baby and spilled it on her hands	
2	F	22	Penicillin and chloramphenicol	Urinary tract infection	500 mg $\times$ 3
3	M	34	Sulphonamid	Bronchitis	250 mg $\times$ 3
4	F	66	None	Ulcus varicosum	500 mg
5	M	52	None	Cholecystitis	500 mg $\times$ 3
6	F	16	None	Bronchitis	250 mg $\times$ 4

Nitrofurantoin

Nitrofurantoin caused reactions in five patients, all of whom were female. It can be seen from Table V that two patients had an exanthematous eruption with *small macules*. Urticaria was observed in one patient, and a severe fever reaction in two. Case 4 had earlier suffered from fever reaction due to nitrofurantoin, and as the drug was given again after a pause two weeks, fixed patches with vesicular spots appeared in the legs in addition to the fever. In Case 5 a temperature reaction of ad 39° C was provoked by 50 mg nitrofurantoin in a few hours.

Nalidixic acid

There was exanthematous eruption in a 63-year-old female with psoriasis after 12 days of treatment.

Trimethoprim

There were two maculopapulous exanthematous eruptions due to trimethoprim. The patients had received a combination of sulphamethoxazole and trimethoprim for the treatment of urinary tract infection. Trimethoprim (40 mg) caused pruritus and mild exanthema after 2 hours in a provocation test.

Tuberculostatic drugs

Para-aminosalicylic acid caused partly vesicular eruption in the light exposed

⁴
10 *Chloramphenicol.*

Time of appearance of the symptoms	Type of eruption	Provocation
2 h	Angioneurotic oedema	Not carried out
1 d	Urticaria	Not carried out
10 d	Urticaria + angio-neurotic oedema	Chloramphenicol +
6 h	Anaphylactic shock	Chloramphenicol +
3 d	Exanthema	Chloramphenicol +
8 d	Lyell's syndrome	Chloramphenicol +

areas in two patients. In one it was observed after 7 months of treatment and in the other after 2 years of treatment.

Etambutol caused exanthema in one case after 25 days of therapy. The patient received INH simultaneously, but tolerated it later on.

Ethionamide caused a fever-reaction and partly vesicular exanthema after treatment for one month. The patient had simultaneously received PAS and INH which he tolerated later on.

2. Analgesics, antipyretics and antirheumatics

Acetylsalicylic acid

Acetylsalicylic acid caused 18 skin reactions. The reactions were observed relatively early after administration of the drug, in 1-6 hours in 5 patients and after 1-3 days in the rest. Erythema fixum, of which there were 9 cases altogether, occurred most frequently. Six of the patients had previously been affected with this drug reaction several times. Two of them had bullous erythema fixum, of which one case was associated with fever and vasculites of the legs, similar to erythema nodosum. Erythema fixum appeared as ulcers in the penis and the anus of two patients.

Urticaria and/or angioneurotic oedema were observed in 6 cases. The tongue and lips of some patients were swollen at the same time. There were 2 cases of exanthema and one erythema multiforme. Provocation tests were carried out in two patients who had taken a preparation composed of several different

TABLE
Drug Eruptions due

Case No.	Sex	Age	Previous drug allergy	Dose
1	F	72	Nitrofurantoin	100 mg $\times$ 2
2	F	38	Sulphonamide	100 mg $\times$ 3
3	F	23	None	100 mg $\times$ 3
4	F	41	None	50 mg $\times$ 4
5	F	59	None	50 mg $\times$ 4

analgesics. Acetylsalicylic acid activated the erythema fixum spots in both patients in two hours.

Salicylamide

Three patients had skin reactions. One had urticaria and two had erythematous reactions. The patient with urticaria had earlier developed this reaction

TABLE
Drug Eruptions due

Case No.	Sex	Age	Previous drug allergy	Time of appearance of the symptoms
1	F	44	Meprobamate	24 h
2	M	20	None	20 h
3	F	37	None	3 h
4	F	51	Acetylsalicylic acid	$\frac{1}{2}$ h
5	F	24	None	6 h
6	F	69	None	1 h
7	M	65	None	24 h

⁵
to Nitrofurantoin.

Time of appearance of the symptoms	Type of eruption	Provocation
6 d	Exanthema	Not carried out
4 d	Exanthema	Nitrofurantoin +
7 d	Urticaria	Nitrofurantoin +
14 d	Erythema fixum Fever	Not carried out
14 d	Fever	Nitrofurantoin +

both due to sulphonamide and acetylsalicylic acid. Provocation tests with salicylamide were positive in all three patients.

Phenazonsalicylate

Phenazonsalicylate caused skin reactions in 7 patients that are displayed in Table VI. There were 3 cases of urticaria, 2 cases of exanthema and 2 cases

⁶
to Phenazonsalicylate.

Type of eruption	Provocation
Erythema fixum	Phenazonsalicylate +
Erythema fixum Stomatitis	Phenazonsalicylate + Acetylsalicylic acid -
Urticaria	Phenazonsalicylate +
Urticaria	Phenazonsalicylate + Acetylsalicylic acid +
Urticaria	Phenazonsalicylate +
Exanthema	Not carried out
Exanthema	Not carried out

of erythema fixum. The skin symptoms appeared generally rapidly— $\frac{1}{2}$ –24 hours after the administration of the drug. Drug allergy was confirmed by provocation tests in four patients (Cases 1–4) who had taken combination preparations.

Phenacetin

Skin reactions were observed in 4 patients. The symptoms appeared in all cases within 7–48 hours. Bullous erythema fixum was noted on the skin of the extremities in 2 patients, and 2 patients presented urticaria and angineurotic oedema mainly in the face.

Aminophenazone

There were 4 eruptions due to aminophenazone. The skin reaction appeared after 2 hours as general pruritus and angineurotic oedema in one patient. Erythema multiforme was observed in 1 patient after 3 days, and Stevens-Johnson's syndrome with severe symptoms developed in two other patients. The skin changes were bullous and haemorrhagic, and in addition to this the conjunctivae and the mucosae of the mouth and the genitals were affected. Provocations were not carried out.

Phenylbutazone

Seven patients with eruptions due to phenylbutazone are more closely described in Table VII. The skin reactions appeared usually after several days of treatment. There were 4 cases of erythema fixum, of which one was bullous and another associated with purpura. There was one case of both purpura and erythema multiforme.

Case 1 with Stevens-Johnson's syndrome had been given a daily dose of 3×200 mg phenylbutazone for 10 days for arthralgia (LED?). Skin reaction was bullous, and all the mucous membranes were affected. Perforation of a duodenal ulcer was an additional complication, after which exitus followed 30 days after he was admitted to the hospital. Erythema fixum of Case 5 relapsed in 24 hours after peroral provocation with 100 mg phenylbutazone. Provocation was not carried out in the other patients.

Oxyphenylbutazone

Five patients had skin reactions. There were two cases of erythema fixum, one of which was associated with ulcerous vasculites in the legs. Two patients had papular exanthema. In addition to this there was one case of erythema multiforme. The daily therapeutic dose of all patients was $100 \text{ mg} \times 3$. One eruption became manifest already after two days of treatment, another after 7 days. The skin reactions of the rest of the patients did not become manifest until after 12–34 days.

TABLE 7
Drug Eruptions due to Phenylbutazone.

Case No.	Sex	Age	Indication	Dose	Time of appearance of the symptoms	Type of eruption
1	M	51	Arthralgia (LED?)	200 mg $\times$ 3	10 d	Stevens-Johnson's syndrome Exitus
2	F	52	Lumbago	100 mg $\times$ 2	4 d	Erythema fixum
3	F	70	Arthralgia	100 mg $\times$ 2	10 d	Erythema fixum (bullosum)
4	M	54	Lumbago	100 mg $\times$ 2	8 d	Erythema fixum (+ purpura)
5	F	66	Rheumatoid arthritis	100 mg at times	2 years at times	Erythema fixum
6	F	56	Rheumatoid arthritis	100 mg $\times$ 3	3 m	Purpura
7	F	40	Arthralgia	100 mg $\times$ 2	7 d	Erythema multiforme

Chlormezanone

There were three cases with three types of reactions: one case of exanthema, one of erythema fixum and one of erythema multiforme. The daily dose was $100 \text{ mg} \times 2$. The skin symptoms appeared after 1-7 days' treatment. Provocation test was carried out in one patient with erythema fixum. Skin lesions of the genital membranes appeared in 5 hours.

Codeine

There were 5 patients altogether, two of which had earlier developed a skin reaction to codeine. One was allergic to mercury. The skin reactions manifested in all cases within 5-24 hours after administration of the drug. Two had exanthema and two urticaria. Erythema fixum occurred as livid red patches on the skin of the penis and scrotum in one patient and bullous stomatitis was observed. The provocation test with 10 mg codeine was positive in the urticaria patient, who had drug eruption for the first time. Provocation was not carried out in the other patients.

Opium tincture

Reaction to this preparation was observed in two patients, one with erythema fixum in the legs and conjunctivitis, another with severe angioneurotic oedema of the face.

Quinine

Two patients with *abusus analgetici* had developed fixed eruptions several times before on the dorsa of the hands, the feet and the penis. Quinine chloride provoked the lesions of both patients within 2-3 hours. Other analgetic components used in provocation tests did not cause any reaction.

Chloroquine

A 28-year-old female received a daily dose of $2 \times 250 \text{ mg}$ chloroquine phosphate for 20 days, which led to the manifestation of Stevens-Johnson's syndrome with mucocutaneous, bullous affections.

Gold

Sodium-aurothiomaleate caused an eruption in 4 rheumatic patients. Gold therapy had been given to one patient for 3 months and to the others for 6 months prior to the manifestation of skin symptoms. The clinical picture was exfoliative dermatitis with features of seborrheic eczema. The eruption generally lasted for months, in one patient up to 2 years after withdrawal of the treatment.

"Analgesics"

Eruption due to different combinations of analgesics and antipyretics, the components of which had not been tested more closely, occurred in 31 patients. Three patients had earlier suffered from sulphonamide eruption, and in 11 patients the present eruption had occurred earlier. Urticaria and angioneurotic oedema were seen in 13 cases, erythema fixum in 8 cases. Purpura occurred in 3 cases and exanthema in two.

Two patients had nodular vasculites in the legs similar to erythema nodosum. One patient had erythema multiforme and Stevens-Johnson's syndrome developed in one case of *abusus analgetici*. One patient had an anaphylactic reaction in 10 minutes after having taken an analgetic that contained acetylsalicylic acid, propylphenazone and diallymal.

*Barbiturates, psychopharmaca and antiepileptics**Phenobarbitone*

Phenobarbitone caused eruptions in 12 cases. One patient had earlier suffered from a drug reaction due to sulphonamide. Skin reactions manifested in 5 patients after 1-7 days of therapy. Others had taken the drug for a longer period, more or less regularly.

Six patients had exanthema. One had exfoliative dermatitis, associated with stomatitis and purpura. The number of leucocytes in the peripheral blood of this patient was 51,900 per μ l, of which 22,317 were eosinophils. Urticaria occurred in 3 cases and purpura in one. One patient had for several years had attacks of erythema fixum on the skin of the hands, cheek and penis. The peroral provocation with 50 mg of phenobarbitone was positive in this patient as well as in 2 with urticaria and 4 with exanthema. One of the two urticaria patients reacted positively also to the provocation with pentobarbitone.

Pentobarbitone

Four patients had skin reactions due to pentobarbitone. There were two cases of erythema fixum, one case of exanthematous eruption, and one of erythema multiforme bullosa. Provocation was not carried out in the latter. A dose of 100 mg pentobarbitone produced a positive result in the other patients.

Mebumal

Mebumal sodium caused an eruption in 3 patients who developed respectively urticaria, erythema fixum bullosum, and exanthema.

Nitrazepam

A 30-year old female, who was allergic to sulphonamides, developed purpural exanthema after having taken 5 mg nitrazepam for two successive nights.

TABLE 8
Drug Eruptions due to Meprobamate.

Case No.	Sex	Age	Previous drug allergy	Indication	Time of appearance of the symptoms	Type of eruption	Provocation
1	M	61	Meprobamate	By accident	1 d	Purpura	Not carried out
2	F	23	"Expectorant"	Insomnia	2 d	Urticaria	Not carried out
3	F	44	Phenazonsalicylate	Insomnia	1 d	Erythema fixum	Phenazonsalic. + Meprobamate +
4	F	46	None	Migraine	3 d	Exanthema	Meprobamate + Acetylsalic. +
5	M	42	Sulphonamide	Migraine	1 d	Erythema fixum	Meprobamate +
6	F	65	None	Headache	1 d	Erythema fixum	Meprobamate + Phenylbutazone -

Meprobamate

Skin reactions in 6 patients are more closely described in Table VIII. Four patients had earlier had drug eruptions. Three patients had erythema fixum, one had purpura, another exanthema and urticaria. The symptoms could be provoked by 400 mg of meprobamate in four patients, including three cases with erythema fixum.

Chlorpromazine

Four patients were admitted to hospital because of an eruption due to chlorpromazine. Two patients had a severe, partly bullous exanthematous reaction on the light-exposed areas. One of them had received a daily dose of 2×100 mg for three months, the other of 3×100 mg for six months before the onset of the eruption. One patient had exanthema after 3 weeks of therapy.

Erythrodermia developed after 9 days of treatment in one patient who had earlier had a skin eruption due to phenphormine and ampicillin. The peripheral blood count revealed 4092 eosinophils and 15,700 leucocytes per μ l. The provocation test in this patient with 50 mg chlorpromazine later on caused an exanthematous reaction. Provocation test was not carried out in the other patients.

Thioridazine

Thioridazine caused a skin reaction in one patient who had received the drug for 4 years. The exanthematous reaction was reproduced by the provocation test.

Perphenazine

Perphenazine caused exanthema in one patient after 7 days of treatment.

Imipramine chloride

Two patients were affected with macular exanthema associated with purpura. One had received imipramine for several years and the other for 14 days. Provocation test that turned out positive was carried out in the former patient with a dose of 25 mg imipramine chloride.

Phenytoin

Drug eruptions due to phenytoin were observed in 6 patients. The skin reactions appeared after 7 days in one patient and only $1\frac{1}{2}$ –3 months after the initiation of the treatment in 5 other patients. There were four cases of exanthema of which one had purpura in the lower extremities, lymphadenopathy, and swelling in the palms and soles. The peripheral blood count showed 10,000 leucocytes, of which 2,277 were eosinophils. In addition to this, two cases of erythrodermia and one with erythema fixum were observed.

Peroral provocation test with phenytoin (50 mg) in five patients was positive.

Provocation test with was not carried out in one of the patients erythrodermia. Three patients had received the combination of phenytoin and phenobarbitone. Phenobarbitone was tolerated by all of them.

Carbamazepine

Ten cases altogether due to carbamazepine were observed. The therapeutic dose ranged between 200–600 mg per day.

Exfoliative dermatitis proved to be a typical form of drug eruption, often associated with vesicular eruption in the flexural regions. The skin of the palms and soles was hyperkeratotic and rhagades developed. This type of eruption was observed in 5 patients (50 per cent). Carbamazepine had been given to these patients for longer periods before the manifestation of the eruption. One patient received it for 12 days and the rest for 3–13 months. The eruption appeared gradually, resembling an eczematous eruptions and it was therefore difficult, at the onset to associate it with the drug therapy.

Four cases of exanthema were observed. The drug therapy before the onset of the eruption had lasted for 2–30 days in these cases. One patient had erythema fixum. The provocation tests were carried out and were positive in two cases of exfoliative dermatitis and two cases of exanthematous eruption.

Ethosuximide caused exanthema in a 5-year-old boy after 18 days of treatment.

4. Other drugs

Iodine

Iodine caused skin reactions in 7 patients. Two patients had hypersensitivity to sulphonamides. There were three cases of urticaria and/or angioneurotic oedema, one exanthema associated with acne, and one anaphylactic reaction. Erythema fixum was seen in two patients. One of these was of bullous type.

Provocation was carried out later on in two patients with urticaria. Potassium iodide provoked urticaria after 6–10 hours.

Chloquinol

Two cases of morbilliform exanthema occurred 24 hours after the administration of the drug. Photosensitivity appeared later on in one patient.

Bromhexidine

A 53-year-old male patient developed urticaria after 10 days of treatment. He had earlier had an anaphylactic reaction to penicillin and urticaria due to both tetracycline and theophyllin. Provocation test was not carried out.

Chlorpropamide

Two patients were affected with exanthema after 2 months of treatment. One of them was according to previous tests, allergic to sulphonamides. Provocation test in which a dose of 250 mg chlorpropamide caused exanthema carried out in the other patient.

Tolbutamide

Exanthema appeared in a 78-year-old female after 6 months of treatment. Provocation test was positive.

Chlorthiazide

This drug caused exanthema in one patient after a daily dose of 500 mg for 10 days.

Cyclophosphamide

A 55-year-old male patient was given cyclophosphamide several times because of carcinoma of the lung. Severe purpura appeared in the lower extremities when he received this drug for 7 days after a pause of one month.

Nicotinic acid

Nicotinic acid caused urticaria in two patients. The result of the provocation test was positive later on.

Pyridoxine

Erythema fixum in association with purpura due to pyridoxine was observed in one patient.

Riboflavin

Urticaria was seen in one patient due to riboflavin.

Xantinolnicotinate

A patient, who had earlier suffered from eruption due to penicillin and tetracycline, was affected with a macular, widespread exanthema after one month of treatment.

Isosuprin-chloride

One case with erythema fixum on both thighs and legs was observed after one week of treatment.

Quinidine

Three cases were observed. One of them had earlier had an eruption due to quinidine and was now affected with exanthema after 24 hours. The skin reactions in the other two patients became manifest 20-40 days after the initiation of the treatment as morbilliform exanthema. Provocation test was carried out in one patient, and exanthematous reaction relapsed in association with it.

Phenindione

Two patients, who had been receiving anticoagulant therapy for 6 months, were affected with partly purpurel, macular exanthema.

Benzocain

One case of urticaria was observed.

DISCUSSION

Cases of cutaneous reactions to drugs have been published from different departments of dermatology, among others by *Heijer et al.* during 1954-58 (104 cases) (17), *Kauppinen & Reckhardt* during 1959-1960 (553 cases) (24), *Lazaro & Cubero* during 1965-68 (344 cases) (26), *Juhlin* during 1966-68 (200 cases) (21), and *Kauppinen* during 1961-1970 (620 cases) (23). The examination of the material presented here does not reveal anything essentially new, but serves as a supplement to earlier studies and may give additional knowledge about certain forms of drug allergies.

Eruptions due to *sulphonamides* (187 cases) formed the major part, i. e. 40 % of the whole material. This number was between 2.4 %-19.3 % in the previously published materials (21, 23, 24, 26). The steady increase of the use of sulphonamides is the obvious reason also for the the increase of eruptions caused by them.

Severe Stevens-Johnson's syndromes (12 cases) and Lyell's syndromes (5 cases), altogether 17 cases, formed 9 % of the eruptions caused by sulphonamides. The number of these reactions amounted to 25 % of the cases in a material of 49 sulphonamide-caused eruptions previously published by the author (25).

The role of sulphonamides in the formation of Stevens-Johnson's syndrome and Lyell's syndrome has been widely discussed (1, 3, 7, 20). It has been proved clearly, however, that long-acting sulphonamides, especially sulphamethoxypyridazine, cause frequently Stevens-Johnson's syndrome (4, 16, 23).

On a food and drug administration survey, *Carrol et al.* reported (11) that by the year of 1966 116 cases of Stevens-Johnson's syndrome in connection with long-acting sulphonamides were reported. By the year of 1968 this figure was 147, the total number of Stevens-Johnson's syndromes due to sulphonamides being 178 (6).

Long-acting sulphonamides are also indicated in several materials as the causative agents of Lyell's syndrome (5, 22). *Kauppinen* showed (23) that 28 out of 36 patients with Lyell's syndrome had been given sulphonamides. 22 of them had received either sulphamethoxypyridazine alone or in combination with sulphamethizole, the preparation of sulphonamide mostly used in Finland. In the present material 103 out of 187 cases of sulphonamide eruptions had been given the same two preparations, including all the five cases of Lyell's syndromes in connection with sulphonamides.

Since 1966 a campaign has been going on for the restriction of the use of sulphamethoxypyridazine and other long-acting sulphonamides. They are recommended to be replaced by short-acting preparations, which seem more seldom to be associated with the above mentioned, severe skin reactions.

Penicillin caused 35 skin reactions (7.5 %). Their number is relatively small compared with the corresponding figures (17-46 %) published on basis of earlier materials (21, 24, 26).

Recently the use on new penicillin derivatives, especially *ampicillin*, has, however, increased, and the number of eruptions due to ampicillin was almost equal to that due to penicillin: 33 cases (7.1 %). Penicillin eruptions were distributed as in previous materials, urticaria, angioneurotic oedema and anaphylactic reactions having the highest occurrence. Con-

versely, macular exanthema often associated with purpura, occurred almost as often due to ampicillin.

It has been indicated that ampicillin causes relatively more skin reactions than penicillin. According to some studies about 10 % of the patients treated are affected (10, 27).

Two cases of mononucleosis, in which ampicillin caused exanthema, were observed in this material. Patel (1967) noticed exanthema in all 13 mononucleotic patients treated with ampicillin (29), and this skin reaction with almost one hundred per cent occurrence has later been discussed in several studies (14, 39).

Phenytoin has several side-effects, the most severe of which are as a rule haematological (15, 28). Also severe skin reactions—Stevens-Johnson's syndrome and Lyell's syndrome—in connection with phenytoin have been described (6, 22, 26). Robinson described (34) a syndrome with exfoliative dermatitis in 8 patients caused by phenytoin. Dermatitis was here associated with lymphadenopathy, hepatosplenomegaly, leukocytosis, and eosinophilia. The symptoms of one case out of 7 in this material resembled this syndrome. Similar haematological changes occurred in one case of erythrodermia caused by phenobarbitone.

According to the literature, *carbamazepine* causes side-effects in 25–67 % of the patients who receive the drug. Gastrointestinal and haematological complications occur most frequently (28). Burke diagnosed pruritic erythematous eruption in 9 patients out of 68 (9). Stevens-Johnson's syndrome and Lyell's syndrome have also been discussed as complications of carbamazepine therapy (19, 22).

The present material contains 10 cases of carbamazepine-eruptions. This is only 2 % of the whole material, but compared with other antiepileptic drugs the number is relatively high, since the use of carbamazepine compared with e. g. phenobarbitone and phenytoin is low.

In five cases exfoliative erythrodermia developed gradually, resembling infectious or seborrhoic eczema. As the symptoms appeared gradually, many had received carbamazepine for

longer periods, before the cause and effect relationship between drug and eruption had been noticed.

Erythema fixum

Erythema fixum—a typical drug reaction that recurs on the same site of the skin when the drug is readministered, has been observed to be due to several different drugs. The most typical causative agent are barbiturates, salicylates, phenacetin, phenylbutazone, sulphonamides, arsenic, antimon, iodine, mercury, and quinine (8, 40, 41). The reaction mechanism of erythema fixum has not been fully clarified (32).

This material includes 42 cases, which is 10 % of all the patients and slightly more than previous materials (24, 26). Most of the cases were caused by the above mentioned, causative agents. More infrequent causes were nitrofurantoin, ampicillin, chlormezanone, pyridoxine, isoxuprinchloride and carbamazepine.

In 1943 and 1944 Sonck described (37, 38) three cases of severe erythema fixum on the skin and the genital regions caused by sulphanilamid. Erythema fixum is very rare as a side-effect of the sulphonamides used today. Among 123 eruptions due to sulphonamides there were only 2 cases of erythema fixum in Kauppinen's latest material (23). No case of erythema fixum was observed between the sulphonamide eruptions of the present material.

SUMMARY

A total of 464 patients, 135 males and 329 females, suffering from drug eruptions were treated in the Department of Dermatology, University of Turku, during 1966–1970. The most common skin reactions were exanthema (214 cases), urticaria and/or angioneurotic oedema (107 cases), erythema fixum (46 cases) and erythema multiforme (25 cases). Nineteen cases of Stevens-Johnson's syndrome and 6 of Lyell's

syndrome were observed. Exfoliative dermatitis, purpura, anaphylactic reactions, photosensitivity, erythema nodosum, and fever reactions were also observed. Two patients died.

The eruptions were caused by more than 50 different drugs, the most common being sulphonamides, penicillin, ampicillin, salicylates, pyrazolone derivatives, and barbiturates. The number of sulphonamide eruptions was 187. Five cases of Lyell's syndrome as well as 12 of Stevens-Johnson's syndrome belonged to the latter group.

The number of eruptions due to penicillin was 35, to ampicillin 33.

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