SULPHONAMIDE RASHES

AN ANALYSIS OF 500 CASES SEEN IN NORTH AFRICA AND ITALY

BY

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Since 1937 it has been widely realized that the administration of sulphonamides by mouth is liable to cause drug rashes, particularly of a photosensitive type (Goodman and Levy, 1937; Ballenger *et al.*, 1937; Hallam, 1939), but it was not appreciated until recent times that the local application of these drugs could produce reactions as serious and lasting in their effects as those caused by oral administration. At one time I was an enthusiastic user of sulphathiazole on the skin, in the form of 5% strength in Lassar's paste or in a water-miscible cream (Peterkin and Jones, 1943). With this drug it was found that straightforward septic conditions of the skin such as impetigo contagiosa rapidly vanished. Only two or three cases of sensitization to the sulphonamide group were noted, and they had been treated with sulphanilamide powder before admission to hospital. These reactions soon yielded to soothing applications, so that sulphathiazole, used in this strength and in this form, was regarded as less liable to cause disagreeable reactions than such well-tried drugs as mercury.

In an active theatre of war, however, sulphonamides are used to a far greater extent than in military or civil life at home, and the relative proportion of individuals being treated with these drugs (for wounds, burns, and septic conditions) is very much higher. There is therefore far more risk of sensitization, and many more sulphonamide rashes tend to be observed abroad, though it is interesting to note that the incidence in North Africa and Italy seemed to be much higher than in the Middle East (Park, 1943; Tate and Klorfajn, 1944a, 1944b).

Since my arrival in North Africa in Feb., 1943, I have been compelled in no uncertain fashion to revise my original view concerning the use of these drugs as local applications. During my first 10 days in North Africa, of the 25 cases evacuated from the forward areas diagnosed as impetigo, no fewer than 15 were cases of sulphonamide-light dermatitis of a severity I had never seen in the United Kingdom. During the period spent in North Africa (Feb. to Dec., 1943) and in Italy (Jan. to Dec., 1944)—i.e., 23 months—over 650 cases of sulphonamide sensitization have been seen. Careful notes have been kept of 500 of these cases.

Under active service conditions it is difficult to obtain access to current literature, but it is believed that so far no paper has appeared describing a considerable number of sulphonamide eruptions and attempting to classify them into various groups, though the book by Bertin and Huriez (1942) must be mentioned as well as the paper by Pillsbury (1944).

Many authors have described cases of the different types of reaction due to the sulphonamides. Shaffer (1943) mentions "contact-type" dermatitis with often widespread vesicular lesions and exacerbation of the original disease, and also refers to scarlatiniform, morbilliform, urticarial, purpuric, vesicular, pemphigoid, pustular, and furunculoid eruptions, as well as rashes closely resembling erythema multiforme, erythema nodosum, and exfoliative dermatitis. Miescher (1943) notes a type composed of erythematous spots on the extremities, especially the extensor surfaces (and sometimes on the face), ranging in size from a lentil to about 2 sq. in.—not sharply

defined but slightly infiltrated. The first mention of the fixed type of drug eruption (somewhat like a phenolphthalein rash) seems to have been made by Loveman and Simon (1939). Costello *et al.* (1942) noted that 21 of 196 cases treated with sulphathiazole developed skin eruptions, erythema nodosum, scarlatiniform, urticarial, and papular rashes, and angioneurotic oedema.

The photosensitization types come into a different group; they seem to be far less common in the United States than in Britain, and very few cases occurred in American soldiers serving over-seas. Despite a close liaison with three U.S. dermatologists, I saw only 5 cases in their patients, though the incidence among Canadian soldiers was as high as in British troops (Hair, personal communication). Sulphonamides were used, if anything, more freely in American patients, but sulphadiazine was more often prescribed than sulphanilamide or sulphathiazole.

Of the various drugs employed, sulphanilamide seemed the most apt to cause reactions, especially if used in the form of the powder, but sulphathiazole, sulphapyridine, sulphadiazine, and sulphaguanidine were often the agents used. The whole group were less likely to cause reactions if applied in the form of a thick paste or a water-miscible cream. In over 90% of cases the original drug which had sensitized the skin was sulphanilamide powder.

Types of Eruption seen in B.N.A.F. and C.M.F.: 500 Cases

	Cases	%
I. Sulphonamide-light	361	72.2
(a) Erythematopapular	47	9.4
(b) Vesicular	1	0.2
(c) Severe—bullous, crusted, and oedematous	309	61.8
(d) Telangiectatic	4	0.8
II. Contact: Vesiculation, followed by weeping and superficial ulceration; maybe general eczematization	51	10.2
III. Infectious eczematoid dermatitis, following a contact dermatitis	31	6.2
IV. Disseminated neurodermatitis—maybe secondary to a patch of neurodermatitis	4	0.8
V. Generalized vesicular	4	0.8
VI. Generalized bullous (pemphigoid)	1	0.2
VII. Fixed type of drug eruption	1	0.2
VIII. Purpuric:		
(a) Generalized—after oral administration	1	0.2
(b) Contact—purpuric reaction	3	0.6
IX. Morbilliform: Often with vesico-bullous eruption of hands and feet	12	2.4
X. Scarlatiniform	3	0.6
XI. Urticarial	3	0.6
XII. Lupus erythematosus	5	1.0
XIII. Erythema multiforme	6	1.2
XIV. Erythema nodosum	5	1.0
XV. Pustular or acneform	4	0.8
XVI. Exfoliative dermatitis	5	1.0

I. Sulphonamide-Light Eruption

(a) *Erythematopapular Type*.—This was the first type of reaction recognized as being due to the sulphonamides, and has been described by Goodman and Levy (1937), Ballenger *et al.* (1937), and Hallam (1939), among others. More recently, excellent descriptions of cases occurring in the Middle East have been given by Park and Platts (1942) and Park (1943).

This eruption may be seen in patients after oral medication or local application. Prior to 1941 the former was usually the cause, and was not uncommonly seen in peacetime in people who had been treated with sulphapyridine, followed by general ultra-violet irradiation as a tonic treatment. The typical dusky-red erythematous-papular rash, limited exactly to the areas exposed to light, disappeared spontaneously in 24 to 48 hours, and the patient did not remain light-sensitive. The type due to local application was rarely seen in civil life, but proved to be moderately common in Army dermatology. It was usually associated with a typical sulphonamide contact dermatitis (see below), and disappeared rapidly without treatment; 47 such cases were noted.

Illustrative Case.—Bdr. A., aged 25. First seen on June 22, 1943. He was admitted to a field ambulance with a gunshot wound of the lower left thigh, which had been treated by his R.M.O. with sulphanilamide powder and a shell dressing. For the next three weeks sulphanilamide powder was applied daily; he was then evacuated to the base, as the wound seemed more septic and a dermatitis had appeared. On June 21 a rash broke out on the face, neck, hands, arms, and knees. On examination he had a typical sulphonamide contact dermatitis of the left thigh, with a characteristic erythematous-papular eruption sharply limited to the exposed areas. In 24 hours the rash on the face and limbs had faded, and by July 5 the dermatitis had healed thoroughly.

(b) *Vesicular Type.*—Only one case of this kind was observed.

Illustrative Case.—Bdr. B., aged 24; admitted to hospital on Sept. 7, 1943. On Aug. 24 he received a kick on the shin while playing football; a superficial graze resulted. This was dressed at his unit with sulphanilamide powder, which was reapplied daily for seven days. On Aug. 31 he noticed small blisters on the back of the hands, and two days later his hands, face, neck, and knees were covered with hundreds of small blisters. He was sent to hospital as a case of smallpox, as there had been one or two cases in the neighbourhood. On examination the original graze was found healed, with a constellation of vesicles around; these were the size of seed pearls, and were exactly localized to the skin to which the dressing had been applied. The exposed areas of the skin—the face, neck (including the upper sternal area), forearms, hands, and knees—were studded with similar vesicles. These had a non-inflammatory base, were quite discrete, and cultures from them were sterile. Otherwise the skin was healthy except for pityriasis simplex capitis and perlèche. With a soothing and mildly astringent lotion (liq. plumbi subacetat. fort. in calamine lotion) the eruption disappeared in five days, but full recovery was retarded by the appearance of boils on the neck. He was returned to duty on Oct. 10, 1943.

(c) *Severe Type—Bullous, Crusted, and Oedematous.*—This was by far the commonest type of sulphonamide rash (309 cases), and accounted for over 60% of the total series. Though not unusual in the U.K., this type seen over-seas was usually of a severity unknown at home. Strong sunlight played its part, yet some of the worst cases were observed in Italy in Jan., 1944, when the weather was extremely cold and bitter, with little sun. It was significant that the syndrome was rarely recognized before the admission of the patient to hospital, the diagnosis usually being "severe impetigo" (often "with cheiopompholyx") or "pyoderma"; thus many unfortunate men were dosed with large quantities of sulphonamide tablets, with deplorable results. A great proportion of the patients were cases of impetigo which had been treated with sulphanilamide powder. The condition is best described by two illustrative cases:

Case 1.—Pte. C., aged 28; admitted Feb. 25, 1944. This patient was a medical orderly in an infantry unit at the Anzio beach-head; from Feb. 14 to 20 his chief duty had been the treatment of wounds with a sulphanilamide insufflator. On Feb. 20 he suddenly developed a crusted oozing rash which covered his face like a mask, accompanied by a rise in temperature (i.e., a sulphonamide-light eruption). This was diagnosed as an acute impetigo, and he was given sulphanilamide tablets (7 g.) during the 22nd and 23rd. His eyes became inflamed, with intense photophobia; the whole face was swollen, and blisters appeared on the back of the hands. He was then evacuated to hospital. On examination the whole of the face and neck was a confluent crusted mass, with oedema of the eyelids and intense photophobia; the lips were swollen, crusted, and haemorrhagic; the back of the hands and the proximal phalanges were covered with a septic vesico-bullous eruption. Though he had been wearing battledress, the areas exposed in summer (arms, neck, and knees) showed slight desquamation. By March 11 the skin was healed but still dry and taut. It was gradually exposed to direct sunlight, which caused a slight recurrence on the 20th, after 20

minutes' exposure, but he was able to tolerate full exposure to the sun for several hours by April 12. He was discharged on April 17, able to bare his body to sunlight for the whole day, and was recommended for indoor duties. He had spent 56 days in hospital. He kept well till Aug. 10, when for no apparent reason he had a violent recurrence. He was readmitted to hospital and sent home by hospital ship.

Case 2.—Gunner O., aged 29; admitted on June 2, 1944. In Oct., 1943, this patient had impetigo, which was treated with sulphanilamide powder; he developed a sulphonamide-light eruption, which healed after three weeks, leaving no photosensitivity. In Dec., 1943, he sustained a slight wound of the arm, and, despite his statement that he was "sulphonamide-sensitive," this was treated with sulphanilamide and vaselined gauze (S.V.G.). The usual rash appeared, and disappeared in four weeks. On June 3, 1944, he was wounded in the right thigh by shrapnel; this time, thinking it would be of no avail, he did not warn the medical officer that he was sensitive to sulphonamides. He had the wound dressed with sulphanilamide powder, and was given 2.5 g. of sulphanilamide. The next day he was sent to hospital with a moderately severe eruption. On admission the face, neck, upper part of the chest, and the hands and arms were covered with a weeping crusted rash, with considerable swelling. The lower lip was raw and cracked. His skin healed well on 1% hydrarg. ammon. in Lassar's paste, applied as a mask and as spreads, and he was discharged from hospital on June 23, tolerant to light. A label was affixed to his pay-book warning that he was sulphonamide-sensitive. He has kept well since.

Treatment of Type 1c

1. *Local.*—It was soon found that many drugs did not suit these cases, while others seemed to act almost as specifics. Saline soaks, ichthyol, but above all the flavine series, were unsuitable. In many instances the application of acriflavine had caused a marked exacerbation, and in five cases the use of this drug had produced a typical sulphonamide contact or light dermatitis in patients who had had this some months before, but who had not had any sulphonamide applied since that time. In this connexion the article by Russell and Beck (1944), pointing out the dangers of sulphonamide-proflavine mixtures in experimental wounds in rabbits, seems to show that each drug enhances the toxic reaction of the other. It was found that in the crusted oedematous phase the most suitable dressing was lead and calamine or lead and zinc lotion, applied as wet dressings at least night and morning. Weak eusol or eau d'Alibour was also helpful. When the skin became less moist, with little oozing and crusting, a mask of 1% hydrarg. ammon. in Lassar's paste proved to be the most acceptable dressing; 2% hydrarg. ammon. often seemed to be too powerful, while the skin did not tolerate greasy applications such as ung. hydrarg. ammon. dil. very well. This 1% hydrarg. ammon. paste healed the skin in two or three weeks, except in the severe cases, and it was then necessary to test the patient's tolerance to sunlight. The face, hands, and arms were therefore gradually exposed to light—on the first day for 5 minutes, the second day for 7 minutes, the third day for 10 minutes, and so on until the patient could bare his whole body for at least four hours to a strong sun. At first the skin was protected by an anti-light cream—quinoline derivatives and phenol salicylate were not available, and quinine sulphate creams proved of little use. The best cream was 5% tannic acid in a tragacanth or a lanette wax cream, which was applied liberally before exposure to the sun. Quercitannic acid, extracted from the cork oak in North Africa, was tried, but proved inferior to ordinary tannic acid. In the healing stage these sulphonamide-light eruptions closely resembled an impetiginized seborrhoeic dermatitis, and the drugs used in this condition were often employed—e.g., gentian violet 1%, silver nitrate 2%, etc. Penicillin cream also proved useful.

2. *General.*—(i) *Vitamin B complex* seemed to be indicated, as the photosensitivity brought to mind a nicotinic acid deficiency, and the crusted lesions of the mouth, the naso-labial folds, and the ears reminded one of a lack of riboflavin. Therefore yeast (in the form of D.C.L. tablets and dried yeast), multivite tablets, and stout were given in maximal dosage. The response was disappointing, though the impression was that yeast tablets seemed to have most beneficial effect. With the dose given the patients felt the "nicotinic acid flush," but the light sensitivity persisted as much as in those cases which were not given extra vitamins.

(ii) *Quinine sulphate and hydrochloride* were given to 20 cases—the doses being 5 gr. thrice daily—as they have been used with some beneficial effect in other dermatoses associated with sensitivity to sunlight—e.g., lupus erythematosus and erythema multiforme. In some cases the skin could tolerate full exposure to light after three or four days, but the photosensitivity returned after stopping the drug.

(iii) *Peptone* (5%, given subcutaneously thrice a week) was used in several severe cases, as its complex components seem to contain a substance or substances antagonistic to the sulphonamides (Heathcote, 1944). It had no effect whatsoever.

(iv) *Vaccines* were employed in many cases, as the predominant growth in every case was *Staph. haemolyticus*; they were helpful in patients with pustules and furuncles, but had no other effect.

(v) *Penicillin*, given intramuscularly, proved to be the most useful drug of all. It was used in a dosage ranging from 500,000 to 1,250,000 units, depending on the severity of the case. So far 23 cases have been treated. The sepsis usually disappeared within five days, leaving a tender healing skin. It had, of course, no effect on the light sensitivity.

(vi) *Sulphonamides*.—It was relatively easy to desensitize patients to the sulphonamides by starting with a tiny dose and increasing it daily. This, however, had no influence on the photosensitization; it was therefore of little practical value, and was discontinued.

(d) *Telangiectatic Type*.—This was seen in 4 cases, and was always the end-result of repeated attacks of a mild sulphonamide-light dermatitis. Two of the patients had been affected for over two years, the others for about four months. All had a typical appearance, somewhat reminiscent of a mild radio-dermatitis—i.e., mottled pigmentation, fine telangiectasia, and early atrophy of the skin—associated with scattered islands of impetigo. One patient had some pre-carcinomatous keratoses. In all cases the condition was localized to the face, the "V" of the neck, and the back of the hands.

Illustrative Case.—Pte. E., aged 24; admitted to hospital on Oct. 21, 1944. Except for mild dandruff his skin had always been healthy. On June 28, 1944, he was wounded through the leg, which was dressed with sulphanilamide powder and then acriflavine. Three days after wounding a spotty rash appeared on the face and arms, which soon became crusted. He noticed that his lips were cracked and swollen. The erythema subsided but the crusting persisted. Various applications were used, and penicillin powder caused an acute exacerbation. On admission he showed pigmentation and telangiectasia of the brow, cheeks, neck, and lips, and odd patches of impetigo on the cheeks and brow. The latter cleared slowly but steadily with 1% gentian violet used alternately with 1% hydrarg. ammon. paste. Because of the atrophic changes he was invalided home.

II. Contact-type Dermatitis

This type was observed in 51 cases. It appears to have been first noted by York (1942), who described the treatment of 96 cases of staphylococcal infection of the skin: one boy with impetigo of the scalp developed a reaction—i.e., "punched-out ulcers appeared at the edge of the lesions," and healed readily on ammoniated mercury ointment.

According to the excellent papers on sulphonamide eruptions by Tate and Klorfajn (1944a, 1944b), this form of sulphonamide sensitivity seemed to be far commoner in the Middle East than the photosensitization type, which was so prevalent in North Africa and Italy. The reaction occurred most often on the limbs, but was seen occasionally on the head and trunk. Once a few cases had been seen a "spot diagnosis" was easily made, and confirmed by taking the history, but 5 cases (already mentioned) were healed sulphonamide dermatitis reactivated by acriflavine. The original lesion—usually a wound or a graze—had practically healed as a rule, and was surrounded either by bullae or, when they had ruptured, by small superficial ulcers, about 1 cm. in diameter, stippling a raw denuded surface. These ulcers were filled with a thin pus, which on culture gave a pure growth of *Staph. haemolyticus*, except for two cases which produced a growth of *Ps. pyocyanea*, with sparse colonies of *Staph. haemolyticus*: the latter cases had the clinical appearance of pemphigus foliaceus, with the typical large flaccid bullae and musty odour.

The ordinary sulphonamide contact dermatitis yielded rapidly to treatment: either wet dressings of lead and zinc lotion or weak eusol healed the ulcers quickly, and a dressing of Lassar's paste or zinc ointment protected the skin during the final healing phase.

Illustrative Case.—Lieut. F., aged 31; admitted to hospital on March 10, 1944. Six weeks before admission he grazed his left elbow while playing football; the injury "went septic," and sulphanilamide powder was applied on three occasions. A marked spread of the infection ensued, so that the whole arm was affected. On examination it was seen that the original graze had healed completely. The whole forearm, from the deltoid to the wrist, was covered with septic blisters and small septic ulcers, with considerable areas of denuded skin. Wet dressings of lead and zinc lotion were applied, and on March 22 the arm had healed, leaving many healed erythematous areas. He was seen again two months later, and his skin had remained well.

III. Infectious Eczematoid Dermatitis Type

This always began as a typical sulphonamide contact dermatitis, but the staphylococcal infection spread as impetiginous or ecthymatous lesions over the limbs, ears, and beard region. Thirty-one cases of this type were admitted; some of these had become markedly eczematized, and thus resistant to treatment. When seen in the early stages, however, the prognosis was excellent, and a speedy recovery was made. This type, like the contact one, is described by Tate and Klorfajn (1944a, 1944b).

Illustrative Case.—B.S.M. G., aged 25; admitted to hospital on March 23, 1944. On Feb. 19 a superficial gunshot wound of the left lower leg was treated with S.V.G. After several applications the wound had almost healed, but the surrounding skin became raw and weeping, with septic bullae and superficial ulceration. The dermatitis spread until the whole leg was involved, and sores and blisters appeared on the arms, ears, chin, and neck. There was no photosensitivity. Both the leg and the secondary lesions healed quickly on penicillin cream (250 units in a lanette wax and adeps lanae cream).

IV. Disseminated Neurodermatitis Type

Only 4 cases of this type were seen; they were precisely similar except that one began after treatment of a wound in the thigh, two from patches of infective dermatitis, and one after sulphanilamide ointment had been applied to a patch of circumscribed neurodermatitis (lichen simplex chronicus) over the sacral region. The application of the sulphanilamide caused a sudden dissemination of erythematopapular lesions with some lichenification on the neck, on the flexor surfaces of the forearms, especially in the antecubital fossae, and on the front of the thighs. None of these cases had any previous history, or family history, of skin disease.

Illustrative Case.—A.B. H., aged 32; admitted to hospital on May 30, 1944. About six months previously he felt an irritation just above the natal cleft, which caused him to scratch the part violently. Gradually the skin of that area became thick and leathery and intensely pruritic. He was seen by his doctor, who prescribed a 5% sulphanilamide ointment. After a few applications the rash spread "all over the body." The appearance on examination was typical of "eczéma neuropathique"; there was an erythematopapular rash scattered over large areas of the body, with some lichenification and pigmentation. On the sacral area was a large thickened plaque of lichen simplex chronicus (Vidal). The patient, though a sailor with an almost heroic record, was a nervous introspective individual, intensely worried about home troubles. The resolution of these played an important part in the clearing of his skin condition, and he was returned to duty on June 20, with practically no itching but some residual lichenification, after treatment with crude gas tar.

V. Vesicular Type

Four cases of the vesicular type of rash were admitted, two being due to oral administration and two to local application of sulphonamides. The prognosis of these was excellent, as the vesicles rapidly disappeared, and the men could be returned to their units in a short space of time. Three were sent to hospital as cases of suspected smallpox: when the vesiculation was localized mainly to the exposed areas the appearance and distribution certainly suggested this diagnosis.

Case 1.—Lieut. I., aged 24. This officer was admitted to hospital on May 28, 1944, for treatment of an attack of bacillary dysentery, for which he was given sulphaguanidine tablets. When he had taken them for two days a vesicular rash appeared all over his body, and vanished in three or four days. A week later the tablets were again administered, and again a precisely similar rash appeared.

Case 2.—Dvr. J., aged 23, Sinhalese; admitted to hospital on May 8, 1944. For 2½ months this patient had had a dermatitis of the back of the left hand after an abrasion. On May 4 this became septic; acriflavine dressings were applied and sulphapyridine tablets (14 g.) given by mouth. On the 5th he developed malaise, giddiness, and a generalized rash, with intense pruritus. His body was covered by a vesicular rash, not unlike variola; the back of the left hand was raw and ulcerated, with marked oedema. In a week the generalized eruption had gone, but the original dermatitis of the hand did not heal completely till June 4. Though no sulphonamide had been applied to the patch of dermatitis the acriflavine had produced a typical sulphonamide contact dermatitis.

VI. Generalized Bullous (Pemphigoid)

Only one case of this type was seen, and only one could be found described in the literature available—that in the paper by Shaffer *et al.* (1943).

Illustrative Case.—Lieut. K., aged 34; Polish officer; admitted to hospital under the care of Major H. C. Johnston, R.A.M.C., venereologist. This patient had contracted gonorrhoea, which his medical officer began to treat with sulphathiazole; after two days a slight rash appeared on the trunk, and the drug was stopped. However, the patient was determined to have sulphonamide treatment, and managed to secure some sulphathiazole in an illicit manner. He took two tablets, and next day was admitted to hospital with a generalized bullous eruption. He was extremely toxic and appeared to be desperately ill. His condition was very much like a true pemphigus, as the rash was entirely bullous, and Nikolsky's sign was positive; lesions were present on the tongue and the buccal mucous membrane. In order to treat his gonorrhoea, as well as any sepsis present, he was given penicillin intramuscularly: after 100,000 units the bullae disappeared, the mouth healed, and the skin was well within 7 days. His general health, however, remained poor, and even after some weeks at a convalescent depot he complained of weakness and lack of energy.

VII. Fixed Type of Drug Eruption

In this series—from Feb., 1943, to June, 1944—only one case of this type was seen, but since that time two other patients have reported with it. The eruption is essentially similar to the fixed erythema due to other drugs, such as phenolphthalein, the barbiturates, and arsenic. Since 1939, when Loveman and Simon described "sulphonamide fixed drug" eruption, several cases have been reported in the literature—by Director (1943), Dostrovski and Sagher (1944), and Freeman (1944), among others.

Illustrative Case.—Lieut.-Col. L. had for some years been troubled with a recurrent antral sinusitis, and obtained speedy relief by taking small doses of sulphanilamide, sulphathiazole, or sulphadiazine. As a rule the drug was used orally, but more recently he had been taking sulphathiazole powder as a snuff. Some months before, three scaly pigmented patches had gradually appeared on the face and chest, somewhat like a discoid lupus erythematosus. Each time sulphonamides were taken the patches became erythematous, swollen, and intensely pruritic. Macroscopic examination showed three circular, deeply pigmented lichenified plaques on the chin, forehead, and chest. The coloration was dark brown, there being no lilac tint and no follicular plugging. A histological section revealed a picture of chronic inflammation—hyperkeratosis, some acanthosis, increase of blood supply, and an intense round-cell infiltration.

VIII. Purpuric

In a severe case of sulphonamide dermatitis it is a common occurrence to observe purpuric lesions, particularly on the legs, but it is definitely unusual for the rash to be entirely purpuric in character. Shaffer mentions that purpura may be met with in sulphonamide eruptions, and I have now seen 8 cases with only a purpuric rash, 3 of these in the present series. Of the 8, one was due to administration of sulphanilamide tablets and the others to the local application of the powder. The rash in each case soon faded, leaving brown pigmentation.

Illustrative Case.—Capt. M., aged 31, was admitted to hospital with an ulcer on the front of the leg; this had appeared suddenly for no apparent reason 10 days previously. The sore was treated by the daily application of sulphanilamide powder. On examination a typical diphtheritic ulcer was seen; surrounding this was a plaque of purpuric skin, exactly square in shape—i.e., precisely the size of the white lint dressing which had been impregnated with the powder.

IX. Morbilliform

This rash is one of the commonest due to the sulphonamides, and usually occurs after oral administration. Though only 8 cases are included in this series, many others occurred in the hospitals in Africa and Italy. The eruption being well recognized by physicians and surgeons, the drug was withdrawn and the rash soon faded, so that the dermatologist did not often have the opportunity of seeing the reaction in full efflorescence. The rash is most pronounced on the trunk as a rule, but may affect all the skin and cause a vesico-bullous eruption of the hands and feet, with intense pruritus. It is precisely similar to the drug eruption due to the barbiturates—e.g., medinal—and, of course, no photosensitization develops.

Illustrative Case.—Sgt. N., aged 28, was admitted to hospital on Feb. 29, 1944, with an extensive infectious eczematoid dermatitis, which had begun after the secondary infection of an abrasion. The arms, legs, and buttocks were affected by crusted septic patches of dermatitis. After initial improvement he had a relapse on March 8, and on the 9th was given sulphanilamide tablets. After 4 g. he

developed a morbilliform rash on the trunk, limbs, and face, with a vesico-bullous eruption of the palms and soles. By the 13th the rash had disappeared except for some pigmentation, and a "gumboil" had suddenly made its presence felt in the lower jaw. Radiography showed evidence of a large apical abscess; the tooth was extracted, and his dermatitis healed rapidly and steadily. His skin two months later was still perfectly well.

X. Scarlatiniform

Only 2 cases of this type were seen, perhaps chiefly because it is an evanescent rash and usually disappears within 24 or 48 hours. The whole body may be affected, but as a rule the trunk is the main site of the eruption. Like the morbilliform, this type does not seem to be associated with photosensitivity, and patients who have had this rash tend to have the same manifestation if sulphonamides are given again.

Illustrative Case.—Spr. O., aged 22; admitted to hospital on March 16, 1944. Thirteen weeks previously he developed a boil on the right ankle. This was treated with S.V.G. for about a week, after which a weeping eruption appeared on the surrounding skin (i.e., sulphonamide contact dermatitis). On March 11, as the leg seemed to be "septic," he was given 5 tablets (2.5 g.) of sulphanilamide. Five hours later a rash appeared over the whole body, and the dermatitis of the ankle became much more pronounced. On admission he was covered with a scarlatiniform rash, and had a temperature of 102° F. The dermatitis of the right ankle was a typical sulphonamide contact dermatitis. By March 24 the leg had almost healed (the scarlatiniform eruption had disappeared by the 19th), but he had developed numerous boils. He was evacuated on the 25th, as beds were urgently required for fresh admissions.

XI. Urticarial

Two cases of acute urticaria after administration of sulphonamides were seen—one after sulphathiazole and one after sulphathiazole and sulphaguanidine. In both the rash faded in two or three days.

Illustrative Case.—Tpr. P., aged 24, was admitted to hospital on June 8, 1944, because of diarrhoea. His story was interesting. About the end of May he sustained multiple but superficial wounds, and was admitted to a casualty clearing station, where he was given sulphathiazole tablets by mouth. The next day a generalized rash appeared, apparently urticarial in nature; it vanished in two or three days. On June 8 he had a sudden attack of diarrhoea, and was transferred to the medical division of the hospital. On the 12th he was given sulphaguanidine, and next day was covered with urticaria, which disappeared in 12 hours. On July 2 he had further diarrhoea; 12 tablets of sulphaguanidine were administered, and in 3 hours the urticaria again erupted, disappearing within 12 hours.

XII. Lupus Erythematosus Type

The 5 cases seen were all patients who had been treated with oral sulphonamides for chest conditions—wounds with infected haemothorax or bronchopneumonia. The rash appeared after at least 30 g. had been given. It was exactly similar to an acute lupus erythematosus, and involved the cheeks, nose, brow, and sometimes the "V" of the neck, with the typical colour, scaling, and follicular plugging, but disappeared except for some desquamation in 7 to 10 days after stopping the drug and applying ichthyol-calamine lotion.

Illustrative Case.—Pte. Q., aged 21, was admitted to hospital in May, 1944, with a severe penetrating chest wound, which had caused an infected haemothorax. He was operated on by No. 2 Surgical Chest Team, and given sulphathiazole by mouth. His general condition improved steadily, but after 28 g. of the drug he developed erythematous lesions on the cheeks and brow, the appearance and distribution of which were most suggestive of lupus erythematosus.

XIII. Erythema Multiforme Type

In 5 of the 6 cases seen the eruption was a typical erythema multiforme, and each patient gave a history of having a sore throat, which was treated with sulphonamides orally. It is possible that the rash might have appeared whether the drugs had been used or not, as the lesions and course of the disease were indistinguishable from true erythema multiforme. One case, however, was somewhat different. This patient was a sergeant who had had severe abdominal wounds which necessitated major surgery. The damage was skilfully repaired; he was given sulphanilamide, but his temperature remained high for no apparent reason. As either a streptococcal or a staphylococcal septicaemia was feared despite sterile blood cultures, the sulphanilamide was stopped and sulphathiazole used instead.

The temperature still remained high, and an erythematous rash appeared on his neck. This was a patch of erythema multiforme. The drug was withdrawn, and in two days his temperature fell, the rash disappeared, and he made an uninterrupted recovery.

XIV. Erythema Nodosum Type

Some of the 5 in this group were quite ordinary cases of this disease, while two showed circinate erythematous plaques which were more superficial than the typical erythema nodosum and were not extremely tender. Similar lesions have been described by Miescher (1943) as occurring on the limbs and face after oral sulphathiazole.

Illustrative Case.—Guardsman R., aged 26, was admitted to hospital with a cellulitis of the leg following an abrasion, and was given sulphathiazole by mouth. Within 24 hours the front parts of the legs were studded with numerous tender indurated erythematous plaques, which gradually disappeared, leaving brown pigmentation. A general examination, including radiography of the chest, revealed no physical changes.

XV. Pustular or Acneform Type

Though Shaffer *et al.* (1943) have described a case of pustular exacerbation of an acne vulgaris after oral sulphathiazole in a man whose skin had been sensitized by the previous use of a sulphathiazole lotion, the 4 cases in this series were all seen as an end-result of sulphonamide medication. The patients had either had a sulphonamide-light eruption, which had disappeared, leaving pustular lesions on the face, or had had a sulphonamide contact dermatitis, which had healed, leaving a persistent folliculitis that had proved difficult to clear.

Illustrative Case.—Spr. S., aged 32, was admitted to hospital in May, 1944, with a sulphonamide contact dermatitis of the left leg. Three weeks before admission he had grazed the calf of his leg on barbed wire, and sulphanilamide powder had been applied daily as a dressing. After 7 days the graze had practically healed, but a weeping dermatitis about 4 in. square developed. This healed rapidly on wet dressings of lead and calamine lotion, but follicular pustular lesions which were present persisted for 7 weeks after the original dermatitis had healed.

XVI. Exfoliative Dermatitis

Many patients, of course, had a complete exfoliation as the drug rash faded, especially in the morbilliform and scarlatini-form types, but in 5 a severe exfoliative dermatitis was produced, chiefly by the combination of local and oral sulphonamides. Some of these took many weeks to get better, and three patients had to be invalided home.

Illustrative Case.—Pte. T., aged 23, was admitted to hospital on March 10, 1943. For three months he had had a "running ear," treated in various ways, including insufflation with sulphanilamide powder. By February the pinna was involved and the eyebrows became crusted. He was admitted to a forward hospital, where the ears were treated daily with sulphanilamide powder and he was given sulphanilamide tablets four-hourly. A severe generalized dermatitis developed, and he was evacuated towards the base. In Dec., 1942, insufflations of sulphanilamide powder had cured his "running ear" in 4 or 5 days. About the end of Jan., 1943, he developed impetigo of both ears; this gradually spread to the face, and he was admitted to hospital in a forward area, where the infection was treated with sulphanilamide powder. The crusting spread rapidly after this (i.e., sulphonamide contact (dermatitis), and he was then given sulphanilamide tablets four-hourly (number unknown). Within 24 hours of swallowing the first tablets his face swelled, with marked oedema of the eyelids, conjunctivitis, and photophobia. The face and neck were crusted and oozing, a mass of blisters appeared on the hands, and a rash erupted all over the body. When first seen, on March 10, 1943, after he had been evacuated towards the base, he had a generalized exfoliative dermatitis, all the skin of the body being raw and crusted and the lips, tongue, and buccal mucous membrane swollen and ulcerated. There were purpuric lesions on the legs, and the scrotum was oedematous and raw. The temperature was 102° F.; pulse rate, 112. Urine: albumin +; sugar -; bilirubin +++; porphyrins -. He was extremely ill and toxic.

Discussion

In the Central Mediterranean theatre skin sensitization due to sulphonamides ranks as an important problem: every patient with a chronic seborrhoeic dermatitis or a particularly severe impetigo has to be questioned closely regarding sudden exacerbation or photosensitization after the application of a powder or ointment or after the ingestion of tablets. In July, 1943,

the Director of Medical Services, A.F.H.Q., B.N.A.F., issued an instruction that sulphonamides should not be used in skin conditions or minor injuries except under the direct supervision of a dermatological specialist. This order was repeated on several occasions, while at a later date surgeons were warned about the dangers of sulphonamide powders for ear disease, and the necessity for avoiding prolonged use of these powders in wounds and burns.

Fortunately, most of the rashes due to internal administration of the drugs soon disappeared, unless the skin had been previously sensitized by local application. Internal medication can precipitate any of the various kinds of eruption, even the contact type, once the skin has been sensitized. Thus the erythematous and morbilliform and the fixed types do not matter greatly. On the other hand, the bullous (pemphigoid) eruption may be a grave illness, and the patient may even die (Kennedy, personal communication), while Shaffer *et al.* report two cases which each took four months to recover. It resembles "butchers' pemphigus," and the patient appears to be extremely ill. The rapid response to a comparatively small dose of penicillin (100,000 units—it was a precious drug at that time) of the single case reported here is definitely encouraging.

The two forms which caused most trouble to the dermatologist were the contact and light eruptions. The great proportion of cases of sulphonamide contact dermatitis healed rapidly with appropriate treatment, but only too often the patients were admitted to hospital with a chronic eczematous process that tended to relapse after apparent cure.

More distressing still were some of the cases which had become photosensitive. The mild erythematopapular type caused little disability, and the light sensitivity soon disappeared. The severe cases, admitted with oedema and crusting of the exposed areas, cheilitis, conjunctivitis, and a high temperature, took weeks or months to recover, and the tendency to relapse was so evident that the greater number were invalided home even though their skins seemed healthy. For example, out of a series of 65 cases, mild and severe, seen in North Africa in 1943, over 20 were sent home from that country; of the remainder, 11 were seen again in Italy in 1944 and invalided home with (1) a recurrence of their light sensitivity, sometimes but not always due to a further use of sulphonamides or acriflavine—5 cases; or (2) chronic eczema—3 cases; or (3) resistant staphylococcal infections (e.g., recurrent impetigo or seborrhoeic dermatitis, chronic furunculosis or folliculitis)—3 cases. These men seemed to have a skin unable to resist staphylococcal infections.

Four patients were seen with the telangiectatic type of sulphonamide-light eruption; their future may also be viewed with some concern, the atrophy, pigmentation, and telangiectasia having the appearance of a radiodermatitis or mild xeroderma pigmentosa rather than a chronic solar dermatitis, though only one had pre-carcinomatous lesions.

It is difficult to assess how long a man will remain sensitive to light. In the mild erythematopapular cases the patient may well be able to tolerate light within 48 hours, while in the worse types men have been seen still photosensitive after 2½ years. The amount of the drug does not seem to play an important part, as some of the worst cases had had only two or three applications of sulphanilamide powder, and some of those who recovered rapidly had been dosed with large quantities of assorted sulphonamides.

The chronic cases do not resemble other light dermatoses, such as Hutchinson's summer prurigo, but are to all intents and purposes cases of chronic seborrhoeic dermatitis with a profuse dandruff, crusting of the eyebrows, chin, and ears, and often flexural seborrhoea. A careful history will elicit the use of sulphonamides and exacerbation on exposure to light localized to the face, neck, hands, arms, and knees.

It was significant that sulphanilamide in powder form was most liable to cause sensitization, but sulphanilamide in vaseline is almost as bad. This drug, probably because it was most commonly employed, was responsible for over 90% of all reactions. Only a few cases were caused by sulphadiazine and sulphaguanidine. Most patients appeared to be sensitized to all the sulphonamide drugs, but occasionally there was a selective sensitization, well described by Park in a recent paper.

The treatment of skin conditions such as impetigo, seborrhoeic dermatitis, and secondarily infected tinea led to the greatest number of reactions:

Dermatoses	62.66%
Otitis externa	4.00%
Wounds	13.00%
Grazes and minor injuries	14.33%
Burns	4.00%
Other diseases (e.g., tonsillitis, appendicitis)	2.00%

It seems impossible to determine what percentage of people treated by sulphonamides locally develop sensitization, but it is interesting to note the experience of other dermatologists in treating skin infections with these drugs. For instance, Pillsbury *et al.* (1941) treated 190 varied cases with no evidence of absorption and no local or general reaction; Kalz and Prinz (1942) treated 130 patients with no systemic effects and no mention of dermatitis; York (1942) had one case of contact dermatitis in 96 cases; the Robinsons (1941), in a series of 48 cases of impetigo, had two cases of contact dermatitis; Glicklich (1942) saw no toxic effects in 42 cases; Ingels (1943) had 10 cases of sensitivity in 300 cases; with microcrystalline sulphathiazole Bigger and Hodgson (1944) had one case of sensitivity in 50 cases treated; of 196 patients treated by Costello *et al.* (1942) 21 had skin reactions—i.e., of 1,052 cases treated 3.5% became sulphonamide-sensitive. Before I abandoned the local application of these drugs, out of 400 cases treated with 5% sulphathiazole paste or cream I observed 4 which developed photosensitization, either mild or severe.

There seems to be little doubt that sulphonamides can be applied to the skin, as Pillsbury (1944) says, with little risk of causing sensitization if the process is not an eczematous one and the drug is used for not longer than 5 days in the form of a thick paste or water-miscible cream; but as diseases such as impetigo can be treated satisfactorily by other methods, it appears that sulphonamides should no longer be used as a topical application.

In 1943 I performed various tests on men with the light eruption. Patch tests gave erratic results, as they were invariably positive on areas previously affected by the rash—i.e., the parts exposed to light—and usually negative on other parts of the skin. Scratch and intradermal tests were rarely used, as they tended to cause (as often happens with these tests) an exacerbation of the original condition.

Complexion had, it appeared, little or no significance in this series of cases—in fact, the rufous type seemed less prone to severe reactions, while the worst cases were seen in men with dark hair and skin. Photosensitization was seen in Indians, Gurkhas, Sinhalese, and men of negro stock.

The incidence of sulphonamide reactions in the U.S. Forces seemed to be much lower than in United Kingdom, Dominion, or Empire troops: light eruptions were rarely seen, but occasionally the other types occurred. Two busy American dermatologists practising during the twelve months of 1944 in the same theatre of war saw in their own group of patients only 4 cases each that were definitely due to the sulphonamide series. Several reasons for this extraordinary difference may be suggested, but the most important are that the commonest way of using sulphonamides locally in the U.S. Medical Corps was in the form of 5% sulphadiazine in a water-miscible cream, and that acriflavine was seldom employed. Not unnaturally, American colleagues were sceptical of the high incidence in British troops until they were absolutely convinced by the numbers of cases shown them.

Summary

From Feb., 1943, to Dec., 1944, over 650 cases of cutaneous sensitivity to sulphonamides have been seen in North Africa and Italy; of these, 500 are reported and classified into 16 various types.

These reactions were due to the treatment of many different conditions, from major wounds and burns to slight grazes, impetigo, and chancroid.

Only 3 of the types described are liable to cause a grave or prolonged illness—i.e., the pemphigoid, the sulphonamide-light eruption, and the sulphonamide contact dermatitis.

Sulphonamide-light dermatitis accounted for 72.2%, and contact dermatitis and its complications for 17.2%—i.e., 90% of the total.

Most cases of reaction were due to the use of sulphanilamide in powder form; the safest drugs appeared to be sulphadiazine and sulphaguanidine.

Acriflavine can reactivate a sulphonamide-light or contact dermatitis just as may cocaine.

No race is exempt from this sensitization—skin colour and texture make little or no difference.

Sulphonamide reactions are uncommon in U.S. troops compared with British.

The local application of sulphonamides is contraindicated in skin diseases, though there is little risk if the drugs are used with certain precautions.

Intramuscular penicillin appears to be the treatment of choice in two types—the pemphigoid and the severe light dermatitis.

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PREVENTION OF SEA-SICKNESS IN ASSAULT CRAFT

A REPORT OF EXPERIMENTS UNDER TROPICAL CONDITIONS

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Assault landings in combined operations entail the transport of large numbers of men in small craft over seas which may be rough. Previous experience in operations (such as the invasion of Sicily) and in training has shown how disabling sea-sickness can be to troops taking part in such landings. In many countries a number of remedies have been tested in the search for a means of preventing or mitigating sea-sickness without impairment of the fighting efficiency of troops when disembarked on the beaches.

From the reports of previous workers it appears that the most efficient remedy is hyoscine (Holling, McArdle, and Trotter, 1944; Holling and Trotter, 1944); other members of the atropine series are less effective. Amphetamine (benedrine) had been claimed by Hill (quoted by Jowett, 1943) to reduce the sickness rate dramatically, but was found by Jowett and Thomson (1943) to be ineffective. A combination of hyoscine with amphetamine has been claimed (Jowett, 1943; Jowett and Thomson, 1943) to be highly effective. Chlorbutol has been found of little value (Holling and Trotter, 1944).