THE SO-CALLED STEVENS-JOHNSON SYNDROME

BY

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The syndrome described by A. M. Stevens and F. C. Johnson (1922) consisted of a generalized eruption, continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis. It remains a rarity.

Controversy still exists about whether it is identical with the condition formerly referred to as erythema exudativum multiforme (Hebra). It has been claimed that cases of this nature were described in France as early as 1822 by Alibert and Bazin (Rosenberg and Rosenberg, 1940), but it was left to Hebra (1866) to attach a name to this group of polymorphous erythemas, which he considered due to a systemic invasion by some unknown factor. He stated that the mucous membranes may be involved, but did not stress the occurrence of conjunctivitis of a serious type.

This form was noted by Mracek (1902) and Crocker (1903), the latter mentioning that the conjunctiva may be the first membrane involved. Dühring (1896), describing over a hundred cases of erythema exudativum multiforme (Hebra), mentioned only mild conjunctivitis. J. H. Bailey (1931), in dealing with his three cases from the ophthalmological standpoint, recognized their similarity to those described by Stevens and Johnson, but also found that they resembled the much earlier cases of Fuchs, 1876; Molenes-Mahon, 1884; Gerk and Kain, 1892; Stark, 1918; Barkan, 1918; Hartler, 1921; and Raffin, 1922. The Commission on Acute Respiratory Diseases (1946) considered that the use of the eponym "Stevens-Johnson" was without historical justification.

The work of Rendu (1916) should be referred to. Under the title "Ectodermose érosive superficielle," he gave an early account of a condition differing little from that described by Stevens and Johnson.

Ginandes (1935) preferred to regard the Stevens-Johnson type cases as conforming to the atypical cases of erythema exudativum multiforme (Hebra), and concluded that a satisfactory designation of these cases would be erythema exudativum multiforme (Stevens-Johnson). He considered that this term would call attention to the unusual features of the condition emphasized by the authors. Among others who contend that the Hebra and Stevens-Johnson types of erythema exudativum multiforme are essentially the same disease are Keil (1940) and Smith (1929).

Modern Cases

The cases of Stevens and Johnson occurred in children aged 7 and 8. Ginandes (1935) described a case and reviewed the nine others that had been reported up to that time. He brought out the startling fact that total blindness had occurred in seven. The other cases had been contributed by C. A. Bailey (1929), Rutherford (1929), and Wheeler (1930). Givner and Ageloff (1941) published their cases as being exceptional in that vision had been retained.

Murphy (1944) described a case in a man aged 22, the second to be reported with penile lesions. In the ensuing cases of Erger (1944), who had reverted to an older name "erythema multiforme pluriorificialis," Kove (1945), and Hoffman and Stone (1948) genital lesions were described on each occasion, and these have come to be recognized as an almost constant feature of the severer case.

The Commission on Acute Respiratory Diseases (1946) published six cases of severe erythema multiforme with evidence of a pulmonary involvement in three, and recognized as a non-bacterial pneumonia. The chief purpose of the report was to emphasize the relationship of pneumonia to erythema exudativum multiforme, since lung involvement was a feature not stressed enough in previous descriptions. The ages of their six cases ranged between 18 and 36 years.

Stanyon and Warner (1945) reported 17 cases of the major form of erythema exudativum multiforme, with non-bacterial pneumonia in 14, including two fatalities. Patz (1947) made a study of six cases, endeavouring to discover a virus. In his cases complement-fixation tests with psittacosis antigen were negative, as also were the findings following intracerebral and intraperitoneal injection of vesicular fluid into rabbits, guinea-pigs, and mice.

Dealing with the relationship between pneumonia and erythema multiforme exudativum, Finland, Joliffe, and Parker (1948) reported four cases and three necropsies. They investigated the cases with a view to discovering any association with psittacosis. In their first case serological examination revealed a positive complement fixation in a dilution eventually reaching 1 in 1,024. A significant rise in psittacosis antibodies was shown in Case 2, and in this and also in the third case there were histories of contact with a sick or dead bird. No inclusion bodies were seen in any of the cases, and virus studies were negative.

Anderson *et al.* (1949), dealing with a solitary case, claim to have found a virus and cytoplasmic inclusion bodies after rabbit cornea inoculation. A recent Continental report of a case was contributed by Scarzella (1949).

In Great Britain cases of erythema multiforme accompanied by severe systemic manifestations have been few and far between. A brief communication by Dowling (1940) drew attention to a group of six cases manifesting erythema multiforme with conjunctivitis, stomatitis, and genital lesions.

Nellen (1947) and Murray (1947) published full reports of cases of erythema exudativum multiforme occurring in this country. Murray's cases occurred in youths of 15 and 16 years.

Other recent English cases have been noted by Sneddon (1947), Johnstone (1947), Neale (1948), and Dresner (1949).

Present Series

In recent years I have encountered several cases of erythema exudativum multiforme. Three of them come into the same category as the Stevens-Johnson type, the others, being much more benign, conform to Hebra's type. The sixth case showed only bullous erythema multiforme, stomatitis, and mild pyrexia. There was no conjunctivitis, but the similarity otherwise to the two lesser cases has induced me to include it as a mild case of erythema exudativum multiforme (Hebra).

It has been customary in the various case reports published on the Stevens-Johnson syndrome to elaborate the negative pathological findings. In the cases here described the Wassermann reactions were negative and urinalysis and blood counts, if within normal limits, have not been dealt with *in extenso*.

Case 1

A policeman aged 27 was admitted to the Royal Gwent Hospital on February 8, 1946, complaining of sore mouth and throat, swollen neck glands, and conjunctivitis. He was a married man with no children.

His condition began with a sore throat three days previously. His voice was hoarse and there was occasional vomiting. Severe ulceration of the mouth developed, his tongue, the inner sides of his cheeks, his gums, and his lips being involved. At the same time the glands in his neck started to enlarge and severe conjunctivitis was present. There was a superficial ulcer on the glans penis and a rash on the back of his wrists and on the front of his knees.

In 1938, while working in a tinplate factory, he first developed sore mouth. Only his mouth was affected, there being no accompanying rash. This cleared up rapidly with simple treatment. He had repeated attacks of sore throat in 1939, 1940, 1941, and 1942. The diagnosis made was Vincent's angina (these may or may not have represented the earliest attacks of erythema exudativum multiforme). In 1943 the mouth ulceration was associated with a rash on his limbs, legs, lower abdomen, and penis. A diagnosis of erythema multiforme was made. He stated that he also had a conjunctivitis. The rash did not extend above the elbows and mainly covered the surface of the arms and hands; it also affected the legs below the knees. The lesions were papular and bullous, and healed in a week, intense irritation being produced initially. Similar attacks were experienced in 1944 and 1945, conjunctivitis being present each time.

On examination his temperature was 102° F. (38.9° C.) and his pulse 128. He showed a dark crusting of his eyelids and also of his mouth. His right eye was inflamed and there was a purulent discharge. The buccal mucous membrane was profusely ulcerated. As regards his skin, a few discrete erythematous nodules were present on the dorsum of the wrists and the fronts of the knees, and there was a superficial irregular ulceration of the glans penis. Swabs taken from the mouth and throat revealed Vincent's angina, and a culture of the pus from the eye grew *Staphylococcus aureus*. The red blood count was normal and the leucocytes numbered 13,900 per c.mm. A slight albuminuria was found. Penicillin therapy was started at once and in seven days his temperature fell uniformly to normal and remained normal. He was discharged on February 26 without further complication.

Case 2

A single agricultural labourer aged 26 was admitted to hospital on February 8, 1949, on account of malaise, cough, and severe skin eruption. There was no history of V.D., and his past and family histories were non-contributory. He said that on January 23 he began to feel hot and out of sorts while at work. On the 27th he returned home and took to his bed on account of what he thought was "flu." Three days later he observed the appearance of red patches on the back of both thumbs and his mouth became sore. Following this his eyes started to lacrimate and to feel irritable, and the genital eruption was first discerned.

After two days on sulphathiazole tablets he was transferred to an isolation hospital. His eruption was spreading, and by February 4 he was found to have an extensive erythema multiforme eruption chiefly of the iris type but with some commencing bullae. By this time he was seriously ill and was transferred to the Royal Gwent Hospital.

On examination he was obviously ill and had a temperature of 102° F. (38.9° C.) and a pulse rate of 104. The skin of the trunk and limbs showed dark-red discrete and confluent lesions of erythema multiforme of both the bullous and the iris forms (Fig. 1). Some of the bullae had ruptured on the back, leaving raw surfaces (Fig. 2). Both eyes showed black, haemorrhagic crusting (Fig. 3). There was a prominent bilateral mucopurulent conjunctivitis. Both corneae were clear. The pupil reactions, fundi, eye movements, etc., were all normal. A similar haemorrhagic crusting existed on both lips, and there was an extensive membranous desquamation of the lining of the mouth, producing much discomfort.

Abnormal physical signs in the chest were not pronounced at this stage, but on auscultation low and medium-pitched rhonchi could be heard. There was inspiratory crepitus at both bases. The genital lesions consisted of a superficial

excoriation extending from the scrotum to the under surface of the penis. There was a purulent balanitis but no urethritis.

Progress

During the four days after admission his condition deteriorated and he became very drowsy. The skin lesions were pemphigoid and raw. Penicillin, 1,500,000 units daily in aqueous solution, was then started, and after two days he seemed

FIG. 1.—Case 2. Distribution of skin lesions.

improved. The eyelid plaques were becoming detached and the bullae over his trunk were collapsed and dry. His temperature was down and he coughed less.

On February 17, however, the twenty-first day of his illness, his chest symptoms worsened and his temperature was swinging between normal and 102° F. (38.9° C.). Next day a patch of pulmonary consolidation was clinically discernible in the left lower zone. An x-ray photograph of the chest showed a diffuse opacity in the left lower lobe due to consolidation. Another opacity was present in the right cardiophrenic angle, due to consolidation of one of the segments of the right lower lobe.

Penicillin was discontinued after 10 days' treatment, sulphathiazole being substituted. Some improvement in the chest signs took place during the next few days, and on February 22 a further x-ray film revealed a small quantity of fluid at the right base. There had been some clearing of the opacity at the right base, and now this area showed a honeycombed appearance. The left base also showed slight clearing. The pain in the chest had almost gone, but considerable languor and some dyspnoea remained.

From the time penicillin had been started systemically and locally the skin lesions had improved steadily, and there had been no tendency for fresh bullae to appear. The most stubborn areas were on the genitals, and these persisted for two weeks after other areas had cleared. Continued rest in bed was advocated until all lung signs had cleared, but, even after a further three weeks, clinical and radiological signs remained

FIG. 2.—Case 2. Appearance of ruptured bullae on back.

FIG. 3.—Case 2. Facial appearance.

and the patient then insisted on leaving hospital after 53 days because he felt so well.

At a later date he was seen in his own home and recovery was apparently complete, but even as late as May 19 examination of the chest revealed some impairment of percussion note and some residual crepitation at the left base. An x-ray photograph showed that there still remained obliteration of the left costophrenic angle, considered to be due either to a very small quantity of fluid or to pleural thickening. A final radiograph in September indicated complete resolution.

Pathological investigations revealed little. The blood count was normal on several occasions and the leucocytes remained at about 9,000 per c.mm. The erythrocyte sedimentation rate was 30 mm. a minute (Westergren). Examination of the sputum for tubercle bacilli was repeatedly negative. Sputum culture on February 8 showed a profuse growth of *Neisseria catarrhalis* and *Staphylococcus aureus*, coagulase-positive.

Case 3

A girl aged 5 was admitted to hospital on November 15, 1949, on account of a generalized skin eruption accompanied by

FIG. 4.—Case 3. Appearance of facial lesions on twelfth day of illness.

a purulent conjunctivitis and a severe stomatitis. Her temperature was 100° F. (37.8° C.) and her pulse 110 a minute. There was considerable prostration.

Ten days previously her doctor had been called in and found a scarlatiniform eruption and a troublesome cough. The temperature was then 102° F. (38.9° C.) and the pulse rate 100. No abnormal physical signs were detected in the chest, and sulphadiazine therapy was instituted. On the following day the rash had almost faded, but diarrhoea had begun. The cough persisted, and three days later some crepitations were discernible in the chest. The temperature was raised a little and the child appeared better. On November 13 there began swelling of the eyelids and injection of the conjunctivae and also soreness of the vulva. Next day she was considerably worse and the skin eruption was observed. The temperature had again risen to 102° F. (38.9° C.) and she was then transferred to hospital.

Physical examination revealed a very ill child resentful of being handled and muttering incoherently. There was a generalized skin eruption. On the face it consisted of confluent erythematous areas surmounted by ruptured bullae on the cheeks (Fig. 4). Irregular erythematous macules were scattered profusely over the trunk and limbs; they were evenly distributed, some of the lesions having central vesicles (Fig. 5).

The thick purulent exudate from the eyes had matted down the lids, but after twenty-four hours it was possible to open the eyes, when photophobia was apparent. There were chemosis and injection of the conjunctivae with very thick purulent exudate. The corneae were not affected. The lids showed erythema only at this stage. The lips and adjacent skin were caked in a dry, rigid dark-red mass. It was not possible to

examine inside the mouth, from the reduced orifice of which a purulent discharge was emerging. On the genitals there were a circumscribed dusky erythema of the vestibule and a thick purulent vaginal discharge.

The blood count indicated 11,200 leucocytes per c.mm. Vincent's organisms were present in a swab taken from the mouth. An x-ray photograph of the chest revealed no abnorm-

FIG. 5.—Case 3. Distribution of skin lesions.

ality. In view of the history of diarrhoea, the stools were cultured and the presence of *Shigella sonnei* was reported.

Penicillin was given locally and systemically. Penicillin eye washes were instituted and penicillin ointment was smeared on the lids. Penicillin cream was applied to the lips and also the genitals. Sulphonamides were withheld at first, but later sulphaguanidine was given for the dysentery without untoward effects. The stomatitis proved to be the most stubborn element, and it interfered with her eating in the early stages. After being in hospital for three weeks, she would have been considered fit for discharge but for the continuing presence of dysentery bacilli in the stools.

Case 4

A girl aged 14 was seen at her home on February 2, 1949. She was complaining of soreness of the eyes and mouth, of an eruption on her hands and one foot, and of a general feeling of being out of sorts. She said that five days previously she had first noticed swelling of the upper eyelids and lacrimation. Next day her eyes had become bloodshot, and on the 4th the skin signs had started to appear on both the backs and fronts of the hands. Soreness of the mouth and lips followed and her face showed some swelling. Her temperature was slightly raised. She felt depressed and had lost her appetite. A previous attack lasted from July 10 to August 7, 1948. It was similar to the present one except that it was considerably worse.

On examination her temperature was 98.6° F. (37° C.) and pulse rate 90 a minute. Her face showed some general swelling (Fig. 6) and there was a purulent exudate from her eyes. The conjunctivae were injected and chemosed. The lips were swollen and showed a superficial ulceration, and there was a stomatitis consisting mainly of a hyperaemia of the buccal mucous membranes. The gums were swollen and brightly erythematous, chiefly anteriorly. The cervical glands were slightly enlarged, particularly on the right side. The skin

FIG. 6.—Case 4. Crusting of the lips and cervical lymphadenitis.

lesions were entirely bullous. Some had serous contents and some haemorrhagic, and a few were mixed.

Sulphathiazole was prescribed and the girl was seen again four days later. At this time she was very much improved and was up and dressed. Her face was not nearly so swollen and no conjunctivitis was evident. The bullae were subsiding, but some new erythema iris patches had appeared in the neighbourhood of the elbows and knees. During the next few days all the signs receded steadily.

Case 5

A supervisor in the Women's Land Army aged 28 was admitted to hospital on September 10, 1949, complaining of a fourth attack of a condition which showed itself as blistering of the hands and feet, redness of the genitals, and conjunctivitis. She stated that two days previously she had had burning and tingling of the lips, fingers, feet, and genitals. A rash appeared on the hands and there was vulval redness. Pain became severe in the hands and itching was unbearable.

Her first attack had come on late in June, 1949. She had taken it for mosquito bites and it subsided after only a few days. The second attack occurred two weeks later with signs on the

FIG. 7.—Case 5. Showing formation of bullae on palms.

lips, hands, and trunk, and vulval "inflammation." A further attack occurred in August, when the eyes were affected for the first time. Of significance was an attack of pain in the back and abdomen, lasting for most of January and February, 1949. There had been frequency of micturition and also haematuria. X-ray examination had failed to reveal any abnormality, and the condition had cleared up with the administration of sulphonamides.

There had been a chronic cervicitis since 1938 with continuing leucorrhoea. Smears were repeatedly gonococcus-negative.

On examination her temperature was 99° F. (37.2° C.) and her pulse 80. Her conjunctivae were mildly injected, but there was no indication of any purulent exudate. A few hyperaemic macules could be discerned on the lips and buccal mucosa. The whole of the palms and palmar surfaces of the fingers showed closely set erythema iris macules, confluent over the thenar eminences and some of the fingers.

Progress.—She had been taking sulphathiazole tablets for two days before admission. After having been in hospital for two days the macules on the hands developed into bullae (Fig. 7), and at the same time three blisters appeared on the lips. The manual and vulval irritation subsided and she felt more comfortable. The conjunctivitis, stomatitis, and vulvitis subsided rapidly during the next five days and she left hospital at her own request. The bullae on the hands were still prominent. The blood count and x-ray photograph of her chest showed no abnormal findings.

Ten days after her discharge from hospital she was seen again and was in excellent general health and spirits. Whereas desquamation was taking place at the site of the original bullae,

further crops of small painless blisters were appearing on the palms of the hands.

Comment.—It was not until one further attack had occurred that light was shed on the causation of this particular case. It appeared that, for her backache, she had retained some sulphonamide tablets from the first time they had been prescribed for her, and had developed the practice of taking them during an attack. On this final occasion she had taken only one 0.5-g. tablet of sulphathiazole, when she began to experience the burning of the eyes, lips, and genitals, and to have red patches on the palms of her hands. She reported at hospital almost immediately, and the relationship between the tablets and the attacks was realized, particularly when she described how, before each earlier attack, she had taken some tablets. On this occasion the erythematous macules did not progress to bullae, and the condition subsided. No further complaint of a similar nature has been reported from this patient.

Case 6

A fitter aged 21 was admitted to hospital on June 22, 1949, complaining of an eruption on his hands and forearms and a soreness and crusting of the lips. His condition had started on June 11 with pale nodules on the skin of the hands. They were particularly sore at first until they formed blisters, which spread as high as the elbows. On June 14 his mouth was first affected.

On examination large bullae were seen on the hypothenar eminences together with dusky erythematous macules over the remainder of the palms. Purplish crusted papules, many of which were septic, were scattered on the forearms. Abundant superficial ulcers were seen on the buccal mucous membrane, and they extended on to the lips. There was a solitary crust on the right lower eyelid. The genitals were clear. At this time his temperature was 99° F. (37.2° C.) and his pulse 76.

He was given sulphathiazole, and after four days his temperature came down to normal and remained so. His blood count was normal and there were no abnormal chest signs clinically or on x-ray examination. He left hospital on July 2.

When seen as an out-patient on July 19 new palmar lesions were present. There were eight small pustules on the palm of the left hand. These also had completely dried in a further seven days.

Discussion

Three of the six cases described (Cases 1, 2, and 3) far exceeded the others in severity. Pyrexia was higher and more sustained, the period of illness was longer, and the clinical manifestations were more pronounced.

Careful study of recorded cases indicates that a division into mild and severe attacks is fairly constant. Reference has already been made to the suggestion by Ginandes of labelling the severe cases as "erythema exudativum multiforme (Stevens-Johnson)" and the milder ones as "erythema exudativum multiforme (Hebra)." The former have also been referred to as atypical cases of the latter. It occurs to me that simpler appellations would be "erythema multiforme exudativum major" and "erythema multiforme exudativum minor." The minor form, as originally described by Hebra, is mainly afebrile, and it involved the skin primarily. The inclusion of "continued fever" as part of their syndrome was stipulated by Stevens and Johnson, and this, together with severe conjunctivitis, provides the main points of distinction between the major and minor types of case.

A recognized feature of erythema exudativum multiforme is its tendency to be recurrent. A consideration of Cases 1 and 4 brings to light the fact that different degrees of severity may be met in different attacks in the same patient.

Before drawing conclusions from these facts, it must be emphasized that neither patient was examined clinically

at the time of the earlier attack. Accepting their histories, however, it then appears that a patient may be prone to major or minor attacks of erythema exudativum multiforme at different periods. Clearly the complaint should bear the same label on each occasion.

The sex incidence is of interest. An analysis in the major cases reveals that it is exceptional for females to be affected, and one of the few reported cases occurring in a female was described by Givner and Ageloff (1941). Patz (1947) states that one patient in five is a female. Case 3 is therefore unusual, particularly in Great Britain. The commonest age is in the early twenties. Pulmonary complications are the most threatening aspect of the condition.

As regards mortality, Lever (1944) was able to collect only four fatal cases before 1944, but many more have occurred since. Finland *et al.* (1948) mention ten deaths in addition to their own three fatalities.

The constant feature is the erythema multiforme, and the lesions are of two types—erythemato-papular and vesiculo-bullous. Attempts have been made to generalize on the distribution of these lesions. The alleged predilection for the dorsa of the hands has not been borne out by the present series—the palms have been mostly involved. Both types of lesion may be present together and the buccal mucosa is invariably affected. The size of the lesions varies within wide limits.

The failure to discover any constant abnormality is now becoming accepted. Blood counts show no marked deviation from the normal, and the examination of the urine reveals nothing further than an occasional febrile albuminuria. Animal inoculations were carried out as part of the Fort Bragg investigations, but no infective agent could be transmitted. Reference has already been made to the researches of Patz (1947) and of Anderson *et al.* (1949). *Staph. aureus* is occasionally recovered from a culture of the sputum. The organisms of Vincent's angina were found in swabs taken from the throats of Cases 1 and 3, and similar results have occasionally been noted in other cases (Chick and Witzberger, 1938). Biopsy has shown only a non-specific inflammation.

The genital lesions do not seem to form part of the general erythema multiforme eruption, but in the male cases they occur as a superficial excoriation on the glans penis and adjacent area of the sulcus and shaft.

Without being in any way specific, penicillin and the sulphonamides have been used in treatment, and quite often the beginning of the fall in temperature coincides with the administration of one or other of these agents. No dogmatic assertions can be made regarding their efficacy.

The fact that the minor attacks in Case 4 proved to be a toxic response to sulphathiazole is revealing. Case 3 had also received sulphadiazine for her initial scarlatiniform eruption. The occurrence of erythema multiforme exudativum following the administration of sulphonamides has been reported by Greenberg and Messer (1943) and Dardinski (1945), who described fatal cases of the syndrome resulting from sulphadiazine therapy. Straus (1948) also observed repeated attacks of erythema multiforme exudativum following the sulphonamide treatment of chancroid. It would thus seem to be proved that the syndrome can be a toxic drug reaction, and it is unlikely that the sulphonamides alone should be incriminated. It also seems likely that erythema multiforme exudativum can be a concomitant of virus and even bacterial infections. The association with herpes simplex (Forman and Whitwell, 1934), mumps (Kove, 1945), and primary atypical pneumonia (Stanyon and Warner, 1945) has already been noted. It may be

that Vincent's angina or dysentery was the primary factor in three of the cases here described.

Summary

A historical account of erythema exudativum multiforme is given.

Published cases in U.S.A. and in this country are briefly surveyed.

Six cases of erythema exudativum multiforme are described, three being of the major (Stevens-Johnson) type and three of the minor (Hebra) type. Two of the cases were associated with Vincent's angina, one with Sonne dysentery, and a fourth was the result of sulphonamide intolerance.

The opinion is expressed that Stevens-Johnson syndrome represents only a severe form of Hebra's erythema multiforme exudativum.

Points of aetiology are discussed and the paucity of constant pathological findings is stressed.

Emphasis is laid on the possibility of non-bacterial pneumonia arising as a complication.

My thanks are due to my colleague, Dr. E. Grahame Jones, for affording me the opportunity of observing and reporting on Case 1 and for much helpful advice. For the photographs of Case 2 and for other related kindnesses I am indebted to my house-physician, Dr. Olewicz. The x-ray reports were made by Dr. T. J. Thomas, whom I also thank.

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Discussing premature babies recently, a W.H.O. committee recommended that a premature baby should be defined as one born alive with a birth weight of 5½ lb. or less. Special units for these babies should be set up where possible. W.H.O. is also sponsoring a statistically controlled demonstration in Iran on the treatment of rabies in human beings bitten by wolves.