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SEVERE ERYTHEMA MULTIFORME

BY

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Numerous papers describing cases of severe erythema multiforme have appeared in American and Continental dermatological literature. There is, however, a scarcity of reports in British journals, the most recent being that of Low and Davies in 1938. The comparative frequency of the syndrome is considered justification for the following case reports. In the early stages the disease may present itself as a sudden pyrexial illness associated with stomatitis which simulates diphtheria, Vincent's angina, glandular fever, or one of the exanthemata. Therefore a knowledge of the condition is of value to clinicians who are not pure dermatologists.

According to Beaudonnet (1894) the first description of the condition is said to have been by Alibert and Bazin in 1822. It has been rediscovered on several occasions, and each discoverer has coined a new name. Thus Fiessinger and Rendu (1917) called it "ectodermose erosive pluriorificielle," Stevens and Johnson (1922) "a new eruptive fever with stomatitis and ophthalmia," and Baader (1925) "dermatostomatitis." Lever (1944) surveyed the literature very fully and concluded that, on the evidence presented, the cases described under the above three names were all the same condition—erythema multiforme. He also suggested that some of the published cases of acute pemphigus and some instances of human foot-and-mouth disease in which laboratory confirmation of the diagnosis was not obtained were also examples of severe erythema multiforme.

I have seen and treated nine cases of severe erythema multiforme in the last four years—one in a child, seven in young adults, and one in a woman of 55. It is therefore not a great rarity. The following cases are described as illustrative of the disease.

Case 1

A single woman aged 25 was seen on Sept. 3, 1946, complaining of severe pruritus ani and vulvae of one month's duration. She had no past history of skin or allergic disease

and her only previous illnesses had been nephritis when 6, and anaemia, which had responded to iron therapy, when 21.

On examination the skin around the anus and vulva was sodden and excoriated, but no underlying cause was found. She was treated with a kaolin lotion containing 1% phenol and a dose of 100 r of superficial x rays to the affected areas. Phenobarbitone was given, 1/2 gr. (32 mg.) in the morning and 1 gr. (65 mg.) at night. The symptoms improved on this regime, and when she was seen again on Sept. 17 the phenobarbitone was discontinued and another dose of x rays given. On Sept. 23 the pruritus vulvae became more intense and the vagina became sore, causing discomfort on micturition. The following day ulcers appeared in the mouth and on the lips; she became feverish and felt ill with headache, backache, and malaise. Towards the end of the day a generalized eruption appeared on the trunk and limbs. On Sept. 25 her temperature rose to 104° F. (40° C.), the eruption became worse, and a bilateral conjunctivitis started. She was therefore admitted to hospital.

On admission her temperature was 102° F. (38.9° C.), pulse 88, respirations 20. Her eyelids were stuck together by a glutinous mucopurulent exudate, her face was swollen and unrecognizable, the whole of the inside of her mouth was covered with a grey sodden pseudo-membrane, and her lips were swollen and crusted. A diffuse eruption consisting of purplish red papules 0.5 to 1 cm. in diameter was present on the trunk, but on the limbs it was frankly bullous. The bullae arose in the centre of papules, and none appeared on normal skin. Both palms and soles showed erythematous macules, with a few flaccid bullae on the tips of fingers and toes. The face and scalp were not involved. Nicolsky's sign was not present. There was a profuse vaginal discharge and the vulva and vagina showed shallow ulceration. The anus appeared normal. There was no enlargement of lymphatic glands, liver, or spleen, and no abnormality was found in the cardiovascular, respiratory, and nervous systems.

During the next four days her fever continued and a number of the bullous lesions became secondarily infected. Micturition was impossible without the help of warm vaginal douches. On the fifth day after admission her temperature returned to normal, her general condition improved, and the necrotic mucous membrane in the mouth began to separate. A few fresh bullae were still appearing on her legs, but most of the papular eruption on the trunk had faded and the conjunctivitis showed improvement. During the next week all the lesions improved rapidly, the ulceration of the lips being the most troublesome and the slowest to heal. She could now pass water without difficulty. On Nov. 15, 21 days after admission, her mouth and lips were normal and all that remained of the skin eruption was faint erythematous staining and slight desquamation. The conjunctivitis had recovered completely and she had no recurrence of the pruritus ani and vulvae.

On Oct. 26 the leucocytes numbered 11,000 per c.mm. (polymorphonuclears, 72%; lymphocytes, 22%; monocytes, 2%; eosinophils, 4%). Blood culture was sterile. Culture from vaginal discharge gave a growth of *β* haemolytic streptococcus and diphtheroids. Culture from the mouth gave a growth of *β* haemolytic streptococcus and *Staphylococcus albus* (coagulase-positive). On Oct. 29 the leucocytes numbered 10,200; on Nov. 5 the haemoglobin was 72%, and the erythrocytes 3,640,000 per c.mm. A skiagram of the chest revealed no abnormality. The Mantoux test was 1:10,000 negative, 1:1,000 positive. Treatment consisted of local symptomatic measures, and after the result of the bacteriological examination 1,200,000 units of penicillin were given intramuscularly from Oct. 28 to Nov. 2.

Case 2

A boy aged 9 was admitted to an isolation hospital on Oct. 14, 1946. For a month prior to admission he had been run down and "nervy." Four days before admission his eyes became inflamed and swollen, and on the same day he bit his lower lip. The lesion on the lip became sore, and ulceration spread to the inside of his mouth. Two days later a few pink spots appeared on his upper chest, his eyes became more inflamed, and blisters were seen inside his mouth. His previous history contained no relevant facts.

On admission his temperature was 100° F. (37.8° C.) and both eyes were closed by swelling and sticky mucopurulent

discharge. The conjunctivae were deeply injected. A purulent discharge ran from his nostrils, which were crusted. His lips were swollen and crusted, the inside of the mouth was covered with a pseudo-membranous exudate, and a mixture of saliva and blood drooled from his lips. Slight enlargement of the cervical glands was present. There was a blotchy erythema on the face, discrete red macules covered the palms and soles, and a purplish maculo-papular eruption was present over the trunk and limbs. A few of the papules on the limbs showed a small central vesicle, but no bullae were seen. No abnormality was found in the heart, lungs, or abdomen. His condition remained unchanged for two days, but then his temperature fell and his general condition began to improve, though at that time a urethral discharge was noticed for the first time. During the next week all the lesions healed except the mouth, which showed shallow ulceration for a few days longer. He was discharged cured 26 days after admission.

On Oct. 16 the leucocytes numbered 10,000 per c.mm., the differential count being within normal limits. Culture from eyes, nose, and mouth showed mixed staphylococci and streptococci, and was negative for *C. diphtheriae* and Vincent's organisms. Culture of the necrotic mucous membrane from the mouth gave a growth of *Aspergillus niger*.

Treatment consisted of penicillin drops to the eyes, penicillin spray to the mouth, and 40,000 units of penicillin intramuscularly four-hourly from Oct. 14 to 20. In addition he was given 40,000 units of antidiphtheritic serum on admission and 10 g. of sulphamezathine in the first 24 hours.

Case 3

An able seaman aged 22 was admitted to a Naval hospital on March 28, 1942. He complained of soreness of the eyes, ulceration of the mouth, and a rash on the arms and legs which had been present for two days. There was no history of drug-taking or of previous skin disease.

Examination on admission revealed severe purulent bilateral conjunctivitis, a grey sodden pseudo-membranous stomatitis involving the inside of the cheeks and the soft palate, and swelling and cracking of the lips. An eruption consisting of pink papules 1 cm. in diameter surmounted by small central bullae was symmetrically distributed on the limbs but did not involve the trunk or face. The spleen was just palpable; this was the only other abnormality found. His temperature was 99° to 100° F. (37.2° to 37.8° C.) for a week, and at the end of this time all the lesions were clearing up. By April 22, 24 days after admission, he had fully recovered.

The leucocyte count on admission was 6,200 per c.mm., with a normal differential count. Culture showed no constant pathogenic organism; Vincent's organisms were not found. Treatment was symptomatic only.

Case 4

An ordinary seaman aged 21 was admitted to a Naval hospital on March 22, 1943, with a history of two days' soreness of the mouth and eyes, cough, backache, and headache. There was no history of previous attacks or of drug-taking.

On admission he had a temperature of 103.3° F. (39.6° C.). Acute mucopurulent conjunctivitis affected both eyes. The whole of the cheeks were covered with a greyish sloughing mucosa, although there was no ulceration or bleeding. Three days after admission he developed a urethral discharge with excoriation of the glans penis around the meatus. On that day also he developed an eruption of large pink papules on the buttocks, thighs, and over the elbows. A few of these papules later developed central bullae. His condition remained much the same for the first week and then began to improve. He had completely recovered on April 20, four weeks after admission.

Culture from the conjunctiva showed no organisms. A throat swab produced a pure growth of *Staph. aureus* but no Vincent's organisms. The urine showed no abnormality. The leucocytes on admission were 23,500, but had fallen a week later to 11,600. The blood Wassermann and Kahn reactions were negative. A total of 29 g. of sulphathiazole and 24 g. of sulphapyridine was given from March 22 to 31, but without any appreciable benefit. Other treatment consisted of lotion and mouth-washes only.

Case 5

A lieutenant, R.N.V.R., aged 32 was admitted to a Naval hospital on Oct. 24, 1943. Four days previously he had had a slight cold in the nose and the inside of his mouth had become sore. This condition had rapidly progressed, and on admission he had gross stomatitis with desquamation of the epithelium over the palate and grey sloughing mucosa over the tonsils. The day after admission he developed a temperature of 101° F. (38.3° C.) and a leucocyte count was 13,800 per c.mm. Sulphamezathine was given, but was discontinued after he had had 13 g., as a red papular eruption appeared on the arms and buttocks. This at first was considered to be a sign of intolerance, but was afterwards recognized as erythema multiforme.

On Oct. 27 an acute conjunctivitis developed and his temperature rose to 103° F. (39.4° C.). The inside of his mouth was covered with sloughing epithelium and the lips were crusted, fissured, and bleeding. His temperature remained swinging between 99° and 103° F. (37.2° and 39.4° C.), and on Nov. 2 he developed a urethral discharge, excoriation of the glans penis, and a pyoderma of the scrotum. The skin eruption was still very evident, and consisted of purplish-red papules, tender to the touch and hot, and confined to the buttocks and extensor surfaces of the arms and forearms. No bullae were seen. Two weeks after admission his temperature settled and all the lesions were by now healing. He was completely well five weeks after the onset. He gave a history of a similar attack in December, 1942, which had lasted two months.

The leucocytes rose to 15,200 at the peak of his illness. The differential count showed 74% polymorphs. The urine was normal, and sterile on culture. A swab from his conjunctiva produced no growth. A swab from the mouth on several occasions gave a growth of *Str. viridans*. There were no Vincent's organisms. Blood culture was negative. Apart from the small dose of sulphamezathine, treatment consisted of local symptomatic measures.

Case 6

A woman aged 55 was seen on Dec. 3, 1946, complaining of the sudden onset two days previously of soreness of the mouth, throat, anus, and vagina, and a skin eruption affecting the neck, trunk, and limbs. Although feeling rather tired for a month previously she had been in good health, and had had no similar eruptions in the past. She admitted taking aspirin occasionally.

On examination she had a temperature of 102° F. (38.9° C.). An acute stomatitis with swelling and cracking of the lips was present. She also had rhinitis with excoriation of the nares, ulceration affecting the vulva and anus, and a profuse purplish maculo-papular eruption on the trunk, limbs, palms, and soles. A few papules had central vesicles. The conjunctivae were not affected. Her condition remained unchanged for seven days and then suddenly improved. Her skin desquamated severely during the recovery phase, but she was normal 21 days after the onset.

The Course of Severe Erythema Multiforme

Severe erythema multiforme is an affection of children and young adults. The onset of the disease is acute, with a temperature up to 104° F. (40° C.), headaches, chill, malaise, and backache. Mucous membrane lesions are the first to appear, and the mouth is usually the earliest orifice to be affected. The primary lesion in the mouth is a flaccid bulla, but it is usually the later picture of extensive stomatitis, with pseudo-membrane which leaves bleeding erosions when it is removed, that is seen. Swelling of the face and the formation of haemorrhagic crusts on the lips add to the patient's misery. Tracheo-bronchial involvement, with the complications of oedema of the larynx and broncho-pneumonia, has been described, but was not seen in this series of cases. Bilateral conjunctivitis occurs in the majority of cases, and is often associated with a rhinitis causing crusting of the nares and epistaxis. Involvement of the genitalia is common and takes the form of balanitis with ulceration of the glans penis, urethritis, and in women ulceration of the vulva and vagina.

Within two to three days of the onset a skin eruption appears. A few cases in which the disease has been confined to the mucosae with absence of cutaneous lesions have been described, but in all the above patients a skin eruption occurred. The eruption usually begins on the extremities, and affects particularly the palms and soles, but at the height of the disease it may be generalized. The eruption is composed at first of macules and papules, but in the severe cases the lesions become bullous. Classical target and erythema iris lesions were uncommon in this series of cases. The disease remains at its height for a week and then the lesions begin to improve and the temperature falls. The conjunctivitis and the skin eruption disappear first and the ulceration of the mouth is usually the last to heal. The total duration of illness is three to six weeks. Unlike the common type of erythema multiforme, relapse is unusual, and according to Lever (1944) if subsequent attacks do occur they are milder. Despite the acute and alarming symptoms the mortality of the disease is low, only four fatal cases having been described in the literature. Complete recovery is recorded in the present cases, but this is by no means the rule, as many American authors have described ocular changes which have led to partial or total loss of vision.

The varieties of ocular inflammation have been well described by Bailey (1931) and Duke-Elder (1938). Duke-Elder describes three degrees of severity—the catarrhal, the purulent, and the pseudo-membranous. The pseudo-membranous conjunctivitis may heal without scarring, but can persist for years, causing conjunctival shrinkage, adhesions between the bulbar and palpebral conjunctivae and corneal opacities. In this stage it is indistinguishable from pemphigus vulgaris affecting the conjunctiva.

Differential Diagnosis

In the early stages of the illness many diseases may be simulated, including Vincent's angina, glandular fever, diphtheria, agranulocytosis, and the common upper respiratory infections. When the skin eruption has made its appearance the field is narrowed and only four conditions have to be considered in the differential diagnosis: drug eruptions, pemphigus vulgaris, dermatitis herpetiformis, and foot-and-mouth disease.

Bullous eruptions may be produced by several drugs, but they rarely affect the mucous membranes and do not usually present this clinical picture, although Moss and Long (1942) described two cases clinically identical with the present ones said to be caused by phenobarbitone. Raffetto and Nichols (1942) and Greenberg and Messer (1943) have also described a similar condition due to sulphadiazine. However, evidence that the drugs were the causal agents is scanty and they may well have been coincidental.

Pemphigus vulgaris is a disease of the elderly; its course is never as acute as erythema multiforme, and dramatic improvement at the end of a week is most unlikely. The eruption of dermatitis herpetiformis may simulate erythema multiforme; but general symptoms are slight, the conjunctivae are not affected, and its course is a chronic one. Human foot-and-mouth disease is a very rare condition, and although descriptions resemble those of erythema multiforme in that conjunctivitis, rhinitis, and balanitis may be present, the skin lesions are confined to the area around the nails of the hands and feet. Laboratory proof of the presence of the virus is now possible by the Waldmann and Pape method.

Aetiology and Treatment

The investigations in the present series of cases have given no assistance in the search for the aetiology of severe erythema multiforme. Leucocyte counts were within nor-

mal limits or slightly raised. Differential counts showed no significant abnormality. Blood cultures were sterile. Bacteriological investigation of the secretions from the mouth and conjunctiva gave growths of only the common pyogenic organisms, and these varied from patient to patient and even from site to site in the same patient. *Aspergillus niger* was cultured in Case 2, but this is considered to be non-pathogenic. Only one of the patients had taken a drug—namely, phenobarbitone—before the illness started. Therefore drugs can be excluded as the main cause.

Most patients complained of feeling off-colour for some weeks before the onset, but no evidence of underlying sepsis or other infection was found. In its predilection for children and young adults, its self-limited course unaffected by therapy, and its benign outcome, the condition bears a resemblance to another disease of obscure origin—glandular fever.

After seeing this series of cases one has the impression of dealing with a definite entity and not just a variety of the erythema multiforme as described by Hebra, and it is not surprising that it has so often been described as a new disease. This is in accordance with French opinions, and the same view is also held by several American authors. However, until there is a more definite lead it is useless to speculate on the probable causal agent.

Treatment.—The disease is self-limiting and treatment has little effect on it. Rapid recovery of the patients after a week's illness has led to claims being made by Weisberg and Rosen (1946) for the beneficial effect of nicotinamide and by Robinson (1945) for the effect of penicillin. However, although it appears to be reasonable to give penicillin for the control of secondary infection there is little evidence that treatment shortens the duration of the illness, which usually improves spontaneously at the end of a week.

Summary

A series of cases of severe erythema multiforme has been described.

The course of the disease, its differential diagnosis, and its treatment have been discussed.

Investigations have failed to throw light on the aetiology of the illness, but it is considered to be a definite entity.

I should like to thank the medical superintendent of the Derby Isolation Hospital for permission to publish the report of Case 2 and the Medical Director-General of the Navy for permission to publish Cases 3, 4, and 5.

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A circular from the Department of Health for Scotland points out that though the majority of old people like to live in their own homes local authorities should help those who are unable to do so. Authorities have the power to provide domestic help in the home if necessary, and to build residential homes for the elderly who are unable to live independently. Not more than about 30 to 40 people should be accommodated in one home, and such institutions should be brightly decorated and comfortably furnished.