J. E. Wolff

OCULAR COMPLICATIONS IN ERYTHEMA EXUDATIVUM MULTIFORME WITH MUCOUS MEMBRANE LESIONS (Pluriorificial Erosive Ectodermosis of Fiessinger and Rendu, Stevens-Johnson Disease, Baader's Dermostomatitis)*†

By

J. E. Wolff

Erythema exudativum multiforme is a specific skin disease of unknown aetiology which may be associated with various syndromes in which the mucous membranes—conjunctiva, lips, bronchi and ano-genital region—are affected, and consequently fall in the domain of the dermatologist, physician, ophthalmologist and uro-genital surgeon. As its name implies, erythema multiforme is characterised by the varied forms of its lesions. Hence no two cases are identical, and owing to the diverse characters of the syndromes a great deal of confusion has resulted in the literature. Authors in various countries had believed that they had discovered a new disease. Hence the multiplicity of names applied to the syndromes, as will be described below. We are in agreement with Sneddon who states that erythema multiforme and its syndrome represent different clinical entities, while Grove and Meisenhelder and others believe the syndrome merely to be a manifestation of erythema multiforme. Several articles on the subject have appeared in the last few years, so that our knowledge of the disease has increased.

A review of the subject shows that as long ago as 1822 Alibert and Bazin (quoted by Beaudonnet) noted that patients suffering from erythema multiforme sometimes presented a conjunctivitis. According to Steffens, Rigler gave the first detailed description of conjunctivitis complicating erythema multiforme in 1852. The name erythema exudativum multiforme was proposed by Hebra in 1866 to denote the erythematous skin lesions while Kaposi used the term "erythema polymorphe." The interesting earlier papers were by Fuchs (1876), Beaudonnet (1894), Düring (1896), Brault and Steffens (1902) and Salus (1912).

The origin of the names "pluriorificial erosive ectodermosis," "dermostomatitis" and "Stevens-Johnson disease" has been traced in the following manner: Rendu (1916). Fiessinger and Rendu (1917) saw a number of acute cases occurring in soldiers on the French front, and to these the name of pluriorificial erosive ectodermosis was applied (see also Berho).

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Some years later Fiessinger, Wolff and Thévenarch (1923), after seeing several more cases, divided the syndrome into two types—I and II. Type I presented the vesicles on the mucous membranes which were always accompanied by a skin eruption of iris-like lesions and purpuric spots, whereas in type II, the skin lesions are absent. The type II may be difficult to diagnose owing to the absence of skin lesions, though the acute onset of fever, stomatitis and ano-genital lesions and conjunctivitis are similar to the first type (de Lavergne).

In 1922 Stevens and Johnson described two cases occurring in children in U.S.A. and since then the syndrome has come to be known as Stevens-Johnson disease in the English speaking world. Many papers bear the title of Stevens-Johnson disease, e.g., Gilbert, Jones et alia, Urniker and Crofoot, Givner and Agelhoff.

In Germany a syndrome exactly the same as type I of Fiessinger was described by Baader in 1925 and since then has been known in German speaking countries as "Baader's dermostomatitis."

The aetiology of the disease is unknown, but four causes have been suggested:

1. E. Ramel suggested that it is due to a haematogenous tuberculous infection, but English investigators (G. H. Percival and H. Gibson; R. Hallum and J. W. Edington) were unable to confirm this by guinea-pig inoculations.

2. A virus theory has been considered by several authors though never proved. N. P. Anderson has discussed the relationship between herpes and erythema multiforme. I. Katzenellenbogen has suggested the use of vaccination in the allied disease of relapsing aphthous iritis.

3. Others have suggested that it is due to a vitamin deficiency, as some cases seemed to improve with vitamin B complex therapy (Adlorsberg).

4. An allergic theory has been stressed by some, because in northern countries the disease occurs most frequently in the spring and autumn. O'Donovan and Michaelson noted that their cases of epidemic kerato-conjunctivitis associated with skin lesions occurred during the rainy season in the Middle East. Bardella and Gandolfi found numerous eosinophils in the conjunctival secretions, but this has not been our experience.

Pathology. Biopsies have revealed a non specific inflammatory reaction.

Age. The disease usually affects people between the ages of 20 and 40 years, but Stevens and Johnson, Storck, Koke, Rosenberg, Wheeler, Edgar and Syverton, Dugan, Ginandes and Landolt have described cases occurring in children.

The disease is usually ushered in by a high fever, headache and prostration which might be severe, and is accompanied by an increase
in the leucocyte count and sedimentation rate. The stomatitis usually follows the onset of the fever, but may precede it in some cases (Murray). It presents three phases as a rule—erythema, vesicle formation and ulceration. A sero-sanguinous discharge or pus may develop. The genital lesions occur both in males and females, and consist of vesicles found on the glans penis and vagina. Nellen's case presented a purulent urethral discharge.

The skin eruption may be papular, macular, circinate, urticarial or haemorrhagic. As a rule it is symmetrically bilateral, with a predilection for the face, arms, legs, and dorsal surfaces of the hands and feet. (W. Stainsby).

The eye lesions of patients presenting a typical picture of erythema multiforme assume a bewildering variety of forms, and one can definitely state that there is no picture pathognomonic of the disease. Consequently the diagnosis has to be made by taking into consideration the entire clinical picture. In some cases conjunctivitis may usher in the disease (Düring, Grove and Meisenhelder).

The lesions vary from a mild conjunctival injection (Cocchi), often limited to the palpebral fissure, to a purulent conjunctivitis. Edmund divided the conjunctival affections into two types:—namely, fibro-membranous and papulo-vesicular. The frequency of conjunctival lesions may be judged from the statement that, of 122 cases of erythema multiforme, Düring reports that three-quarters showed signs of conjunctivitis. Vesicles, nodules, papules and pustules may form on the conjunctiva, and all forms may be present at the same time. Steffens, Terson, Nicolau, Düring, Beaudonnet and Barnett have described vesicles occurring in their cases, and both Steffens and Terson thought that it was a characteristic lesion of erythema multiforme.

Nodules have been noticed by several authors (von Benedek and Müller, Cottini, Alajmo, Bergmeister), and Alajmo studied a histological section which showed a lymphocytic infiltration. Von Benedek and Müller noted that the nodules in one case were situated at the limbus. Chaillious, Nobl and Steffens noted papules. Kubik noted papules, pustules and nodules in his two cases. A pseudo-membranous conjunctivitis is a relatively common complication, and Fuchs noted in a histological preparation of the membrane superficial, parallel layers of hyalin material, then a layer of fibrous exudate containing epithelial cells and round cells. Hanke's section was similar.

Cicatricial contractions of the conjunctiva occurred in our case to be described, and were also noted by Lever, Barkan and others. Symblepharon may form later.

In many cases the cornea is respected, but as in case I, corneal ulcer with perforation may occur. Loss of vision after perforation
### Differential Diagnosis of Polymorphous Erythema, aphthous fever and relapsing aphthous iritis.

<table>
<thead>
<tr>
<th>Erythema exudativum multiforme</th>
<th>Fiessinger-Rendu 1917</th>
<th>Stevens-Johnson 1922</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical type</strong></td>
<td><strong>Type I</strong></td>
<td><strong>Type II</strong></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td><strong>Erythema-vesicular</strong></td>
<td><strong>Erythema-vesicular</strong></td>
</tr>
<tr>
<td>eruption (relapsing)</td>
<td>(relapsing) eruption</td>
<td>eruption especially</td>
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<tr>
<td></td>
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<td>seen on extremities</td>
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<tr>
<td><strong>Mucous membranes</strong></td>
<td>Lesions of all the mucous membranes, including anus and bronchi</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Erythema-vesicular and erosive lesions of all the mucous membranes</td>
<td>—</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>Conjunctivitis-catarhal, or papular, vesicular or pseudo-membranous, rarely an infiltrative or ulcerative keratitis, episcleritis, keratoconjunctivitis sicca</td>
<td>Catarrhal conjunctivitis, corneal infiltrations</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>Slightly elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Both</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>20–30 years</td>
<td>—</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>Leucocytosis (mononuclear) increased sedimentation rate</td>
<td>Leucocytosis increased sed. rate</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>No leucocytosis; sed. rate increased; hypoglycaemia, change in seroglobinulin ratio</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2–5 weeks</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Various factors (intoxication, infective allergy)</td>
<td>Known virus</td>
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### Ocular Complications

- Papulo-pustular erythema or nodular erythema
- Aphthous lesions of lips and anogenital region
- Relapsing iridocyclitis with hypopyon, optic neuritis

**Note:** The table provides a differential diagnosis for Polymorphous Erythema, aphthous fever, and relapsing aphthous iritis. Each condition is compared against historical descriptions by Fiessinger-Rendu and Stevens-Johnson, along with a differentiation of classical types and their associated signs and symptoms.

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has been reported by Bailey and Wheeler. Raffin's case developed a Descemetocèle, the picture being complicated by a rhinitis as well.

Episcleritis is rather rare, but has been reported by Morax, Burnand and Lever. Hartley noted enlarged preauricular glands in one of his cases. Other complications will be described later.

The prognosis: all except one of Sneddon's cases recovered completely, but we feel that a guarded prognosis should be given in view of late sequelae which may occur.

The disease must be differentiated from ocular pemphigus, and recurring exudative iritis. It is easily diagnosed from the former, as pemphigus occurs in older patients as a rule, and has a protracted course, whereas erythema multiforme has an acute onset and recovery takes place from 3-5 weeks (Grove and Meisenhelder). The differential diagnosis is given in summary form in a table after Mach, Babel and Naville.

We now wish to present two cases which are follow-up studies, and have been noted in previous papers from our clinic by Mach, Babel and Naville, and later by Babel and Martin.

Case I.—Mrs. A. M., born 1920. At the age of 20 years she became feverish, and a papulo-vesicular eruption appeared on her skin. A bilateral catarhal conjunctivitis followed, accompanied by desquamation of the conjunctival epithelium. A corneal ulcer developed in the left eye, followed by perforation and incarceration of the iris. Complete recovery occurred in 2 months, except for an adherent leucoma in the left eye (Figs. 1 and 2).

In 1942 she returned to the Clinic complaining of bilateral ocular irritation. The lids of both eyes presented an identical condition—thickened, spongy and heavy, especially the upper lids. The lid margins were slightly inverted, causing some of the lashes to rub on the bulbar conjunctiva and the cornea. The bulbar conjunctiva, except for a slight redness due to that trichiasis, appeared normal. On the contrary, the tarsal conjunctiva was thickened, very injected, and there were dense scars running parallel to and 2 mm. from the lid margin.

Left cornea—thickened opacity in the inferior quadrant with anterior synchia. Slit-lamp examination after fluorescein had been instilled into the conjunctival sac revealed some rather superficial erosions and desquamation of the conjunctival and corneal epithelium. Lacrimal secretion was slightly diminished. The entropion and trichiasis was corrected and the patient recovered.

In November, 1947, patient returned to clinic. Vision 2/50. Operation for division of anterior synchia was performed on November 12, 1947. On November 22, 1947, Professor Franceschetti performed a corneal grafting operation, and the cornea is clear, March, 1948; vision 0.3 with correction (Fig. 2).

Case II.—Mrs. O. R., born in 1897. Nothing of importance in family or personal history, except for usual diseases of infancy.

On May 25, 1943, she suffered from a severe depression after the sudden death of her husband. On June 11, 1946, her temperature rose to 39°, and she developed a frontal headache. On the following day, it was noticed that her cervical glands became enlarged, and she complained of pain on swallowing, photophobia, lacrimation and rhinitis. On June 13, 1946: generalised exanthema, herpetic lesions in the throat, stomatitis, with slight oedema, expectation of abundant mucus without coughing, oliguria, and constipation.

On June 14, 1946, the patient was admitted to the medical wards of the Hospital (Prof. Roch), with a temperature of 40°2° and an eruption of small spots on the face, trunk, knees and hands. On the face there was a tendency to confluence, on the arms there were slightly raised macules, in some of which a central vesicle later formed. The face was puffy, the lips swollen and dry, numerous small ulcers on
the buccal and pharyngeal mucous membranes, covered by a greyish pseudo-membrane and surrounded by an erythematous zone. Palpebral oedema. Severe injection of the conjunctiva with a moderate catarrhal secretion. Cervical glands enlarged and painful, but no other enlarged glands were found. The anal and vaginal mucosa were also swollen and studded with small ulcers.

FIG. 1. (Case 1).—Photograph of the back of the legs showing typical erythema exudativum multiforme.
The cardio-vascular, pulmonary, neurological and urino-genital systems were normal. The various conditions thought of were: severe measles, severe polymorphous erythema, leptospirosis, a toxic or allergic eruption.

**FIG. 2.**
(Case 1).—Photograph of the left eye after corneal graft.

**FIG. 3.**
(Case 2).—Photograph of the right eye showing scars and symblepharon of conjunctiva.

The cervical adenopathy disappeared in 1 week, though the temperature remained elevated. The skin commenced to desquamate. On June 30, 1946, the temperature was subnormal and on the buccal mucous membranes—large plaques dark, red in colour, which bled easily on touching, were noted. The cutaneous elements took on a café...
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Panophthalmitis may occur. Examination of the secretion revealed no pathogenic organisms.

Blood pictures: W.R. negative.

Slight increase in sedimentation rate.

Slight increase in icteris index.

Agglutination for various type of leptospira negative.

Paul-Bunnel test negative.

Calcium: 9'6 mgm. %.

W.b.c.'s: 3'900'000.

R.b.c.'s: 9'500 on June 14, 1946; 3'100 on June 18, 1946; 6'300 on July 10, 1946; 7'800 on June 26, 1946.

Mononuclear: 36 per cent., slight eosinophilia.

January 12, 1947: R.b.c.'s: 4'200'000; Hb.: 48 per cent. C.I.: 1. W.b.c.'s: 4'800; 50'5 per cent. poly neutrophils; 7'5 per cent. immature forms, 1 per cent. eosinophils; 0'5 per cent. basophils; 29'5 per cent. lymphocytes; 11 per cent. monocytes.

Urine: Intermittent traces of albumin and sugar, some leucocytes. No microorganisms found in skin lesions. Inoculation into the cornea of a rabbit: negative.

On July 31, 1946, the patient was discharged from the hospital, her general condition being good. In the beginning of August, we noted for the first time some infiltration in the centre of the right cornea, and intense mixed injection of the right eye, moderate injection of the left eye. The abundant secretion presented the following characteristics: thick, whitish, viscid filaments. No micro-organisms or inclusion bodies. Staph. albus on culture. Vision 1/10 on both sides. A mild irido-cyclitis more marked on the right side was present. In September the secretion remained the same. The Meibomian glands easily visible, and their ducts were enlarged. The corneal ulcer had commenced to heal. The irido-cyclitis bimanual test disappeared on the left side, but there was still some K.P. on the right side. A symblepharon was noticed forming near the punctum of the right lower lid. The appearance of whitish bands, 1 mm. from and parallel to the lid margins was noted. In October, though the cornea had healed, deep vessels began to invade the parenchyma. The conjunctival bands did not progress, but the abundant secretion continued. In December a similar invasion by blood vessels of the left cornea occurred. This eye had in the meantime suffered from an attack of irido-cyclitis while the right irido-cyclitis had almost completely disappeared. The conjunctival secretion became a little less profuse. On installation of Bengal rose and fluorescein tiny ulcers became apparent in the conjunctiva and corneal epithelium. The lacrimal secretion became almost completely abolished.

At the time of writing the condition has become stabilised. The lids are still thickened, there is a slight viscid secretion on the right side. The corneal ulcer and uveitis have gone. The conjunctival scars and symblepharon remained stationary.

Summary

A review of the literature has revealed that almost any ocular complication can occur in the syndrome of erythema multiforme from a mild injection of the conjunctiva most marked in the palpebral fissure, a catarrhal conjunctivitis, a membranous or purulent conjunctivitis. Younger people seem to be more prone to the purulent type. Corneal involvement is comparatively rare. Finally, panophthalmitis may occur. Lesions affecting the conjunctiva
appear to be the most frequent sequelae of the disease, and one should watch the patient for a long time lest symblepharon should occur. An accurate prognosis is thus impossible, and our experience has not borne out the statement that the mucous membrane lesions are always benign (Genet and Speckmann). Herpes ophthalmicus, which is almost certainly due to a virus, is known to affect every ocular tissue, and if the erythema multiforme syndrome is also due to a virus, while the organism shows a predilection for the mucous membranes, it may affect any tissue.

While the aetiology remains obscure the treatment is necessarily symptomatic. Reports of the use of vaccination are too scanty to permit any judgment on its effect. Sulphonamides and penicillin may assist in preventing or curing secondary bacterial invasion. Corneal grafting may be performed. It was done in the first case described in this paper, and we believe it to be the first time this operation has been performed for corneal lesions due to erythema multiforme. These remarks have been illustrated by the description of two cases.

Case I returned to our clinic two years after an acute attack complicated by the development and perforation of a corneal ulcer in the left eye, presenting a trichiasis due to entropion, and small dense scars in the tarsal conjunctiva. The entropion was corrected, and three years later she returned. Corneal grafting was performed, and the vision, which was 2/50 owing to a leucoma, is now 0.3 with correction. We believe this is the first time a patient has undergone the operation for leucoma complicating erythema multiforme.

Case II presents several interesting features. The first attack occurred at the age of 49 years, whereas the disease most commonly attacks people of the 20-40 year age group. The patient’s general condition was very grave. Chest complications are very rarely encountered, though two other cases have been cited—one of Kove’s patients who was gravely ill developed a broncho-pneumonia, and Nellen’s case a transitory pulmonary consolidation. The recurrent attacks of irido-cyclitis resembled those which occur in relapsing aphthous iritis (Behcet’s syndrome)—vide table of differential diagnosis. The alteration in the lacrimal secretion and the punctate staining on instillation of Bengal rose and fluorescein is typical of kerato-conjunctivitis sicca, but unlike the “idiopathic” form, this complication was presumably due to involvement of the secretory glands of the conjunctiva. This complication is not unknown because Richards and Romaine, Richards and Grossmann have reported kerato conjunctivitis sicca as a late manifestation occurring in cases of erythema exudativum multiforme.
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Conical contact lenses—i.e., contact lenses having haptics in the form of a truncated cone—were designed and first produced by Dr. William Feinbloom, of New York, who described them in an article in the "Optometric Weekly" in 1945. Dr. Feinbloom stated in that article that the major problem in contact lens fitting has always been that of reducing to a minimum the pressure of the lens on the eye. He was using Zeiss ground lenses with spherical haptics prior to 1930, and read a paper dealing exhaustively with this type of lens at the American Academy of Optometry meeting in Omaha in 1930. After ten years' experience with this type, he changed over to the moulding method, which he described in a paper at the Academy meeting at Chicago in 1936.