ERYTHEMA EXUDATIVUM MULTIFORME IN CHILDHOOD

BY

A. V. NEALE, M.D., F.R.C.P.
(From the Department of Child Health, University of Bristol)

Hebra (1860) entered into a friendly rivalry with the English dermatologist Robert Willan in his classical dissertations on the 'polymorphous erythemata.' Even in these early years dermatological nomenclature had reached a complex state. Hebra comments that 'these various names by no means answer to as many distinct diseases, and our object must be to determine which of them apply merely to appearances developed in succession during the course of one and the same disease, and, in reference to this, experience has taught me that E. papulatum, E. tuberculatum, E. annulare, E. iris, E. gyratum are merely forms of the same disease according to the period of its course; to this malady I shall apply the name E. multiforme.' The phases and transitions are clearly described by Hebra and some emphasis is placed upon the regional distribution of the rash, it appearing initially on the dorsum of the hands and feet, being in severe cases more generalized even to include, in exceptional cases, the trunk and face. In Hebra's description E. papulatum represents the lowest and E. gyratum the highest grade in the eruption, and he deprecates the notion that these are different species. Also, E. exudativum multiforme may give rise to trifling subjective disorder, fever being observed only in exceptional cases and in those in which the affection spreads over large tracts of the surface and having a duration of up to four weeks. Hebra agrees with Willan that vesicular forms of the eruption may appear, but he refuses to agree that there is any relation with Herpes; and he concludes his masterly clinical description in confessing his complete ignorance of the cause of these erythematous, although his experience indicated a preponderance of these affections in young persons.

It is of some historical interest in this connexion that Hebra (1860) discusses E. epidemicum, aedodynia (which Alibert says prevailed in Paris in 1828), and classifies it as an exudative erythema. Two years later, Bazin (1862) described vesiculo-bullous stomatitis in association with multiform cutaneous lesions.

It is evident that in the following years there was much dispute in regard to the classification and etiology of the erythematous dermatoses. We now understand that individual susceptibility and reaction is indicated by a wide variation in clinical response, and this is specially so in the cutaneous and mucosal surfaces, which in their display of colour, form, shape, and distribution rarely fail to demand careful clinical scrutiny. Whilst, therefore, for certain practical reasons, many of the skin reactions arising out of general disease retain their original and historical descriptive names (which may or may not bear any clear relation to the known etiological factors in the particular case), it has not been entirely favourable in general observation in disease. Dermatological aspects have inclined to dominate description or to cause publication of cases of more general interest in relatively isolated and specialized literature. This trend in using terms according to local signs has undoubtedly led to considerable confusion, and this is specially pointed out by Levy (1947) in his observations on the ' Stevens-Johnson ' syndrome. In this, a group of signs and symptoms have received widely divergent names according to the viewpoint of the observer, or to certain variations in clinical character in individual cases. There is undoubtedly reasonable cause to gather together a group of disorders wherein particular cutaneous and mucosal responses are variably associated, and whilst the ingenuity of some of the names employed, for example dermatostomatitis, mucosal respiratory syndrome, mucocutaneous fever, etc., is recognized, none appears to be sufficiently definitive for continued use. It seems advisable to retain the name E. multiforme and to qualify the term according to additive phenomena. As Stannus (1947) points out, there are wide clinical variations in the disease, and the Stevens-Johnson syndrome belongs to or is part of the condition usually regarded as E. multiforme. Whilst Hebra in 1860 regarded E. multiforme as a primary cutaneous disease with relatively benign effects, it is clear from the literature since his day.
that associated visceral pathology is not unusual and that severe illness is by no means rare. Fies-
singer observed the syndrome characterized by a
vesiculo-bullous eruption involving the mucous
membranes, including the anal and genital regions
and associated with fever and leucopenia.

Stevens and Johnson (1922) claim description of a
'new eruptive fever associated with stomatitis and
ophthalmia': the notion that it is new is probably
unreal in the light of the historical facts outlined by
Keil (1940) and mentioned by Levy (1947). How-
ever, no doubt Stevens and Johnson were so very
impressed by the startling clinical appearances in
their two cases in children that they were convinced
of their unique character. In their clinical summary
they note the generalized cutaneous eruption 'not
conforming to any recognized dermatologic con-
dition,' and in both cases there was a purulent
conjunctivitis. In one of the boys this proceeded
to panophthalmitis and total loss of vision. In the
other boy severe corneal scarring resulted. A high
and continuous fever was present in each case, with
evidence of pulmonary involvement in one child but
not so in the other. The onset was with fever,
and the eruption showed identical characteristics in
each, the rash appearing on the back of the neck
and the chest, spreading to the face, arms, and legs
during a period of about eighteen days, the last
lesions to appear being on the soles and the palms
at about the time when the first eruptive zones were
showing resolution. The eruption showed oval
dark red to purple macules which in a few weeks
were raised firm brownish purple papules 0.5 to
2 cm. in the longest diameter, without pain or
pruritus. Some foci may reveal a yellow necrotic
centre. On the forearms and shins the lesions were
smaller but more thickly disposed. There were no
pustules. The scalp was uninvolved, but the mouth
and lips were intensely sore and inflamed, and
bullae appeared early on the oral mucosa. Resolu-
tion of the skin lesions was evident after three
weeks, and residual faint pigmented areas, without
pitting or scarring, were seen. Fall of temperature
coincided with the period of resolution which
finally involved the forearms and legs six weeks
from the onset.

Baader (1925) observed dermato-stomatitis with
pseudodiphtheritic ulceration of the lips and
sublingual surface and similar scrotal erosion.
Forman and Whitwell (1934) noted that herpes
simplex often precedes an attack of E. multiforme.
They suggest that a virus infection may be the cause
of E. multiforme of the Hebra type.

Ageloff (1940) stresses the possible ocular mani-
festations. In his cases of E. multiforme bullousm,
severe involvement of the eyes called for urgent
selective treatment. In girls, vaginitis may be
present. Schlesinger (1904) considered that the
disease is relatively more severe in children.

We are indebted to Keil (1940) for a comprehen-
sive historical and clinical survey of E. multiforme,
ERYTHEMA EXUDATIVUM MULTIFORME

185

pyrexia. There was considerable conjunctivitis and
the mouth and tongue were covered with superficial
ulcers and sloughs, and the lips swollen. Blistered
appeared on the penis and scrotum and similar
lesions all over the surface, in largest numbers on
the face and extremities. The temperature declined
steadily and after eleven days' illness the child
recovered.' Dowling regards E. multiforme as not
a rare type of cutaneous reaction in the epidemics
of winter sore throats but that the clinical severity
in this particular group was unusual and the appear-
ance of large numbers of bullae suggested pemphigi-
gus; even variola was suspected.

Raffetto and Nichols (1942) suspected that
sulphadiazine was an aggravating factor in a girl
aged ten years who developed, eight days after acute
tonsillitis, generalized vesiculo-bullous eruptions
with oral and conjunctival lesions. In this case
there was 20 per cent. eosinophilia.

A similar but fatal case with oral necrosis is
recorded by Dardinski (1945). Soll (1947) con-
cludes from observations on twenty cases that
sulphonamides should be avoided owing to the
eruptive manifestations. Phenobarbitone is regarded
by Moss and Long (1942) as a possible cause of
severe toxic eruptions affecting the skin and the
mucosal surfaces and closely resembling E. multiforme
exudativum.

Of nearly 72,000 patients in a large infectious
diseases hospital in Manhattan, twenty-eight cases
of E. multiforme bullous were recognized, all
showing multiform erythematous cutaneous lesions,
bullous formations in the skin and mucous mem-
branes, and constitutional symptoms compatible
with acute infectious disease. Most cases were
children under ten years of age. Fever, sore throat,
headache, vomiting, and anorexia, together with
ocular, gastro-intestinal, respiratory, and genito-
urinary symptoms were present. The principal
cutaneous lesions were dark red macules and
papules proceeding to vesicles and large bullae.
To a less extent generalized erythema, pustules,
purpura, crusted lesions, desquamation, and iritis
occurred, and conjunctivitis appeared in moderate
degree. There was some evidence of concurrent
respiratory infection, and three cases were fatal.
In this series Fletcher and Harris (1945) give special
consideration to differential diagnosis. Consider-
able confusion was evident in the pre-admission
diagnosis, haemorrhagic varicella or variola being
suspected, and only one case in the whole series was
correctly diagnosed before admission to hospital.

The bizarre nature of the disease is further
illustrated by the studies of Stanyon and Warner
(1945), who under the term 'mucosal respiratory
syndrome' describe prostrating febrile illness with
mucosal involvement as conjunctivitis, membranous
stomatitis, dermal eruptions, urethral lesions, and
pneumonia. The initial symptoms were like
influenza, with upper respiratory infection followed
by lung lesions resembling the common atypical
pneumonia. Bacteriological studies were essentially
negative, although a virus was isolated in two cases.
Of great interest is the fact that cutaneous eruption
was present in only about half the cases, although
there was no reason to doubt the common etiology
in the series. When present, the skin lesions were
very distinctive, being confined to the forearms,
dorsum of hands and feet, legs, and scrotum. The
stomatitis was usually an early and dominant
symptom. In their fatal cases these authors found
a certain distinctive pathology in the visceral and
buccal mucosa but no specific infective agent could
be isolated. The evidence was suggestive of a virus
disease; attempts to transfer the disease to animals
were unsuccessful. The Commission on Acute
Respiratory Disease note also the prevalence of
non-bacterial pneumonia, with essentially mono-
nuclear reactions, in either the erythemato-popular
or the vesiculo-bullous forms of E. multiforme
exudativum.

In New York in 1947 (Williams) a considerable
increase in the incidence of E. multiforme was seen
after vaccination. In these cases there was incon-
spicuous oral and no conjunctival lesion. The
usual interval was ten days. This phenomenon
was also observed by Schwartz and Brainerd (1946)
to follow five cases of smallpox vaccination, one
case of tetanus toxoid injection, and in one case after
inventing influenza virus vaccine. In such patients
the E. multiforme response occurred at an interval
of ten days. These observations lend some support
to a suspected virus-allergic relationship in E.
multiforme.

Diagnosis

From the descriptive literature as first outlined
by Hebra (who apparently did not record the
presence of mucosal lesions) and later more elabor-
ately discussed by a long series of observers, a
picture of the bizarre manifestation of this disease
may be obtained, but direct inspection of the patient
is the only means of acquiring a clinical memory of
the remarkable appearances usually presented. As
Keil relates, the clinical pictures may be dominated
by systemic disorder, varying as a rule with the
intensity of the muco-cutaneous effects. Initially
an upper respiratory coryzal infection or a sore
throat, mild tonsillitis, pharyngitis and laryngitis,
and a local lymphadenopathy may precede the
exanthema by a period up to two weeks. Painful
throat, dysphagia, and foetor oris may supervene.
Severe coughing and possibly blood-tinged sputum
may follow. The external areas of the nasal
passages may be intensively irritated, and accom-
panied by discharge. Pyrexia may range to 105° F.,
and even the papular forms of the disease
may be associated with considerable pyrexia. No
cardiac changes have been detected. Gastro-
intestinal effects are minimal, and abdominal
examination is usually negative. Eosinophilia has
been recorded in a few cases, but there are usually no significant haematological findings. Haematuria may be due to erosive effects of the urethral and preputial vesicular ulceration.

Respiratory infection may arise as an extended disorder from the oral and nasal ulcero-necrotic changes or, as specially noted in the Canadian cases, primary consolidating disease in lungs may be present of a type resembling atypical pneumonia with mononuclear cell reaction.

Soll (1947) considers that cases may be divided into three groups based upon the severity and distribution of the lesions (a) as originally described by Hebra and including mild forms primarily involving the skin and showing minimal systemic disturbance or mucosal effects, (b) an extremely severe form with extensive lesions on the mucous membranes, cornea, conjunctiva, and omenous possibilities of panophthalmitis, (c) an intermediate type with most effects visible upon the mouth and other mucous membranes and a special tendency to urethritis and balanitis. Nellen (1947) relates a very characteristic example of erythema exudativum multiforme bullosum with ecchymotic conjunctivitis, stomatitis, and urethritis, and in which, after one week's illness with high fever, vesicles on an erythematous base appeared over the extensor surfaces of the arms and legs and soon the patient presented a florid picture, pus pouring from the eyes, mouth, and urethra.

The ophthalmological manifestations in E. exudativum multiforme may vary from mild hyperaemic changes to a severe pseudomembranous form in which disastrous results may arise out of corneal ulceration. There is usually considerable swelling of the eyelids with oedema and vesicle formation, and this is well illustrated in Nellen's paper. Duke-Elder (1938) notes that Fuchs (1876) first recorded the ocular involvement, or 'herpes iridis conjunctivae,' in a case which showed typical skin and oral lesions.

In a recent paper, Sneddon (1947) agrees that the eruption at the maximal phase of the disease may be generalized, but usually in the early stages the extremities, including the palms and soles, are involved, macules and papules being followed in the more severe cases by bullae. He notes that the classical target and erythema multiforme lesions were uncommon in his cases and that, unlike the common erythema multiforme, relapse is unusual. Subsequent attacks, however, may appear with months' or years' interval and with any or all of the previous signs, but usually with a lessened intensity. Membranous sloughing in the mouth may be particularly severe, as in the two boys reported by Murray (1947).

**Etiology**

The disease has many of the features of a primary infection. Acute upper respiratory inflammatory disorder may open up channels of entry and an interval of up to two weeks in such cases may represent an incubation period or a phase of latency in the development of cutaneous and mucosal susceptibility. The association of a virus type of pulmonary lesions in some of the cases is probably very significant and is supportive of the growing evidence in relation to virus infection in erythema exudativum multiforme. Attempts to transfer the disease to animals have so far been unsuccessful. It is significant that in their fatal cases Stanyon and Warner (1945) found in the visceral and buccal mucosa a distinct pathology suggestive of a virus disease, but no specific infective agent could be isolated. The occasional appearance of the syndrome after toxoid or vaccine injection suggests infection and allergy as operative agents. Biopsy of the skin by Nellen revealed non-specific inflammatory changes. Vesicle fluid gave negative reactions for variola and vaccinia antigens (Murray). Much of the primary pathology, especially in the mucous membranes, may be quickly changed by secondary infection, and more especially with staphylococci. Probably extended study with viruses will yield more positive information.

**Case 1.** A boy aged four years had had no previous illness. An attack of mild respiratory disorder with sore throat had begun two weeks previous to the appearance of 'spots on the legs,' which were shortly followed by a similar eruption on the legs, face, chest, and back. The wrists became painful. In another twenty-four hours the rash became haemorrhagic. The mouth was sore, reddened, and very oedematous, and there was some blood-stained mucous in the throat. The clinical picture on admission to hospital was somewhat startling and clearly indicated an unusual disorder. The boy had a pallid,uffy face with considerable oedema; suffusion and haemorrhagic eruptions were present in and around the conjunctivae. The mouth and lips were very swollen, intensely sore, and discharging haemorrhagic secretions. The tonsils and pharynx were hyperaemic. On the face, arms, feet, buttocks, and thighs a haemorrhagic papulo-bullous eruption was present, the maximum distribution of the rash being rather peripheral and chiefly on the extensor aspects. There was pain and swelling of the joints, especially the knees and wrists, and moderate effusion appeared in the left knee. There were no abnormal cardiac or pulmonary signs, and the nervous system was normal. The spleen was not enlarged, and abdominal examination was negative. Blood examination showed no abnormality apart from a slight neutrophil leucocytosis. There was no eosinophilia.
Fig. 1.

Figs. 1 and 2.—Maximum phase of the eruption, Case 1.

Fig. 2.

Fig. 3.

Figs. 3 and 4.—Maximum phase of the eruption, Case 2.
Note confluence and vesicular formation on the face and forehead.

Fig. 4.

PLATE V
During the following week the rash did not extend, but at points of decubitus pressure a deepening necrosis threatened in some of the haemorrhagic areas, especially on the olecranon and gluteal parts. Anything more than temporary pressure indicated a special susceptibility to subcutaneous tissue damage. The swollen joints gradually subsided in about ten days. No nodular swellings occurred. Fortunately there was no spread of the conjunctival eruption to the ocular structures, and although the facial swelling cleared slowly the clinical course of the illness was markedly abating after fourteen days. A mild, simple albuminuria quickly cleared. This boy had no signs of urethral or genital affection, although it is possible that a transient melaena occurred in the earliest phase. Penicillin, 15,000 units three-hourly, was given over a period of ten days, with the primary object of preventing or combating secondary coecal sepsis. (See figs. 1 and 2.)

Case 2. A boy aged seven years entered into an acute illness with high fever, restlessness, and moderate delirium. His eyes and mouth quickly became sore. Dysphagia and cough were troublesome. Difficulty in micturition was associated with acute bullous eruption in the visible urethra and prepuce, with considerable local swelling. Five days from the first symptoms the boy was intensely miserable, the eyes, mouth, and skin being distressful, and in fact all the visible mucous membranes were in acute exudative eruption. The clinical impression was, however, that the boy was not dangerously ill, as he appeared unexpectedly alert on occasions. The skin showed erythematous patches varying in size from \( \frac{1}{2} \) in. to \( \frac{1}{2} \) in. of irregular shape with central vesicle, and being principally disposed on the limbs and the face, the scalp and back being significantly free. Both anterior and posterior surfaces of the limbs were affected and a few papules were present on the hands and feet. Most of the skin lesions blanched on pressure. There was bilateral purulent conjunctivitis with the lids encrusted with thick purulent exudate, but the cornea and other ocular structures did not appear to be involved. Some bleeding foci were seen in the nasal mucosa, and the mouth presented membranous sloughs, especially on the inner cheeks and tongue, which bled easily on local swabbing. There was no visceral abnormality. Blood count was quite normal, and there was no eosinophilia. After six days the exudative reactions showed early resolution, but dysphagia proved troublesome owing to the pain and immobility of the oral structures. Penicillin, 20,000 units at three-hourly intervals, was given as a protective measure, although no pyogenic bacteria were found in the nasal or oral material. (See figs. 3 and 4.)

**Discussion**

The varied and somewhat bizarre descriptions surrounding the disease type initially recorded by Hebra are an indication of the many ways in which clinical description may differ when dominant manifestations may be present in distinctive tissues. The "scattering" in medical literature is no doubt due to the variety in leading signs, which is probably in reference to the factors of primary virus infection, special tissue reaction (especially ectodermal), anaphylactic-like phenomena, and secondary sepsis. In the form of erythema under review some importance is attached to clinical accuracy, especially in regard to possible ocular, oral, or cutaneous resemblance to other conditions. Special difficulty may arise when, as is sometimes the case, the skin effects are minimal and the clinical state is essentially that of acute involvement of the mucous membranes of the mouth and of the conjunctiva. Panophthalmitis with perforation of the eye must be regarded in nearly all cases as the worst possible danger, and especially so in young children. The absence of vesicular or bullous changes and the quick variations in distribution should distinguish E. marginatum. Polymorphous rashes, usually about joints, but sometimes with a more generalized tendency and a secondary haemorrhagic appearance with minute vesicles, are observed in the Henoch-Schönlein syndrome. It is of considerable interest that, in one case, joint swellings were recognized during the acute phase of the illness. There was, however, complete absence of any abdominal symptoms.

The condition of the membranes of the mouth may cast a possible suspicion of diphtheria, although the bullous changes in the mucous membranes and lips clearly dispose of the possibility.

Perhaps some resemblance may exist in regard to variola, and in fact confusion has occurred occasionally. Certain atypical forms of smallpox may have to be considered when papular lesions, however few, quickly acquire vesicular, pustular, or haemorrhagic changes, and especially when such lesions are disposed more particularly about the face, forehead, backs of the hands and feet, and the wrists. Increasing familiarity with the syndrome of E. multiforme of the type discussed in this paper should, however, soon dispose of essential difficulty. Although many of the patients pass through their illness without significant danger, careful watch must be kept on certain possibilities, and probably in the order of importance as (1) conjunctival disease spreading to the ocular structures, (2) progressive ulceration in the mouth favouring descending respiratory sepsis, (3) pressure effects on the skin leading to a deepening necrosis.

**Treatment.** It is in relation to these more severe possibilities that treatment is particularly directed to the affected mucous membranes and the eyes.
Whilst penicillin probably has beneficial action against secondary staphylococcal infection, sulphonamides are better avoided in view of the aggravating effects which have been strongly suspected in some of the cases reported. Neller noted that sulphamethazine was without favourable effect in the severe phase, but general improvement followed penicillin intramuscularly. In a boy bearing the clinical features of E. multiforme bullosa, with marked oral and ocular signs, the disease was apparently aggravated by sulphathiazole, and, in fact, this was considered to be the determining factor in the fatal termination. Nicotinic acid therapy is considered favourably by Weisberg and Rosen (1946).

The photographs in this paper were taken by Mr. J. Gregory Williamson, to whom I am extremely grateful.

REFERENCES
Virchow, R. Erlanger.
Year Book of Dermatology and Syphilology (1946). pp. 252 and 256. Chicago.
Erythema Exudativum Multiforme in Childhood

A. V. Neale

*Arch Dis Child* 1948 23: 183-189
doi: 10.1136/adc.23.115.183

Updated information and services can be found at:
http://adc.bmj.com/content/23/115/183.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/