EPIDERMOLYSIS BULLOSA IN THE NEWBORN

BY

IAN C. LEWIS, ELUNED M. STEVEN and JAMES W. FARQUHAR

From the Royal Hospital for Sick Children, the Elsie Inglis Maternity Hospital and the Department of Child Life and Health of the University of Edinburgh

(RECEIVED FOR PUBLICATION DECEMBER 20, 1954)

Epidermolysis bullosa is an intractable skin condition characterized by the development of vesicles and bullae spontaneously or as a result of minimal trauma. It is usually hereditary and appears to be due to a congenital defect of skin structure.

It has been divided into a simple or non-scarring type inherited as a Mendelian dominant trait and a dystrophic or scarring variety of greater severity, in which the mode of inheritance is variable. Both forms may occur in infancy, and in addition Herlitz (1935) has described a further type which is invariably fatal and very rare.

Since relatively little has been published on this disease in the neonatal period in this journal, six cases are being presented which have been seen recently at hospitals in Edinburgh.

Cases 1, 2 and 3 are examples of the rare Herlitz type, and Cases 4, 5 and 6 of the more common dystrophic variety.

Case Reports

Case 1. T. McC., a boy, the third child of unrelated parents, was born spontaneously at full term in the Elsie Inglis Memorial Maternity Hospital, Edinburgh, after a normal pregnancy on October 3, 1952.

At birth, there were raw, red areas over the wrists, hands and feet, and along the extensor surfaces of the legs. The nails were long and horny. Within 24 hours further bullae containing sterile, straw-coloured fluid appeared over the sacral region. Nikolsky's sign was absent. The Wassermann reaction was negative in parents and child.

Subsequent progress was marked by the formation of widespread bullae over many parts of the body, including the buccal mucous membrane.

The infant's temperature on the fourth day rose to 104° F., and remained high subsequently despite therapy which included penicillin, streptomycin, chlortetracycline and oxytetracycline. *Staphylococcus aureus* was cultured from some of the later lesions. By the fourteenth day hoarseness of his cry and dysphagia were attributed to bullae in the larynx and pharynx.

The bullae healed without scarring in approximately

seven days but fresh lesions appeared and the child's condition became poorer. However, the original raw areas that were present at birth had not healed when the child died. There was no leucocytosis and the blood chemistry was normal except for hypoproteinaemia. Urine analysis was negative, including examination for porphyrins.

Local measures, such as vaseline gauze dressings, kept the skin lesions reasonably clean but the infant continued to deteriorate (Fig. 1) and he died on January 10, aged 10 weeks.

FIG. 1.—Photographs showing skin lesions in various stages about two months before death. (Case 1.)

At necropsy there was widespread extensive epidermal ulceration, particularly severe over the thorax and abdomen. Bullae were still evident and varied in size from minute pin-head structures to large confluent vesicles. No involvement of the pharynx or alimentary tract was found. Post-mortem examination failed to reveal any specific pathological changes affecting the

internal organs and this was confirmed microscopically. Death could not be ascribed to any particular process and so the assumption remained that bacteriological or biochemical factors were ultimately responsible.

Sections of skin were taken from many diverse sites. These sections showed bullae in numerous stages of development (Fig. 2), the larger packed with polymorph

ruptured and released seropurulent exudate, which on culture produced a growth of *Staphylococcus aureus*. Respiration was embarrassed by a blood-stained purulent nasal discharge. The infant was transferred to the Royal Hospital for Sick Children, Edinburgh, on December 7. There were extensive raw areas over the trunk, especially the buttocks, and on the limbs from which a seropurulent

FIG. 2.—Skin section of Case 1 $\times 35$, showing early bullous formation and separation of dermis.

FIG. 3.—Photograph showing extensive skin involvement in Case 2.

leucocytes and obviously infected. The bullae appeared to begin in the stratum Malpighii just external to the basal cell layer, and consequently this layer together with the rete pegs remained intact—a feature that would account for the absence of scarring. The vesicles in enlarging had extended laterally, splitting the stratum Malpighii and finally coalescing as the thin intervening cellular partitions were ruptured. No inclusion bodies could be demonstrated.

In the dermis there was no specific pathological change, sections showing an apparently normal elastic element. Sweat glands were normal and serial sections failed to reveal any direct connexion between these glands and the epidermal bullae.

The stain for elastic tissue was Weigert-Van-Gieson's.

Case 2. D.M., a boy, was the first child of a consanguineous marriage (the parents being full cousins) born spontaneously at full term in the Simpson Memorial Maternity Pavilion, Edinburgh, after a healthy pregnancy on November 7, 1947. On the fifth day vesicular and bullous eruptions occurred in the napkin area and on the extremities, the lesions rapidly coalescing. The blisters

fluid exuded (Fig. 3). Fresh bullae continued to appear on these areas and also on the lips.

The Wassermann reaction of both parents was negative.

The organisms cultured from the lesions being penicillin resistant, he was given systemic and local streptomycin therapy. He was nursed exposed. His temperature became remittent after tending to settle initially, and continued until his death on December 25 at the age of 7 weeks. Throughout his illness there was a moderate leucocytosis. Other therapy was tried both systemically and locally to combat infection and to provide protection but the child's condition progressively deteriorated.

At necropsy, in addition to the extensive skin lesions, bilateral bronchopneumonia was found secondary to aspiration of the gastric contents. No special studies of the skin histology were made.

Case 3. G.M., a boy, was the fourth child of the same parents. Again pregnancy and delivery had been normal but this time the birth was at home on February 21, 1953.

Blistering of a thumb and the umbilical area was said

to be present from birth and further bullae developed rapidly despite the local application of gentian violet. The infant developed 'snuffles' and on admission to the Royal Hospital for Sick Children, Edinburgh, on March 27, many intact as well as broken and secondarily infected bullae were present over the trunk and limbs, on the lips and in the mouth. There was a mucopurulent nasal discharge. Syphilis was excluded and antibiotic therapy was instituted. The child was nursed exposed, but despite this and other local measures deterioration was progressive and further bullae developed (Fig. 4).

FIG. 4.—Photograph of Case 3 just before his death.

He ran a remittent fever but there was no leucocytosis. Terminally, the nails of the hands and feet became detached or deformed and he died in his tenth week on April 28.

At necropsy there were large raw areas on the skin over the occiput, elbows, abdomen, buttocks, sacrum, legs and heels. Some of the ulcerated areas were covered with dry crusts, others had a slightly moist, bright red surface. No bullae remained. The skin, even where intact, was easily torn.

There was a blood-stained serofibrinous effusion in the right pleural sac. Both lungs contained large areas of consolidation: in the heart a roughened area on the posterior cusp of the tricuspid valve may have been the site of a thrombus that had become detached. Antemortem thrombus was found in the left ventricle attached to the chordae tendinae and anterior cusp of the mitral valve. There was a recent infarct in the spleen.

Bacteriological examinations revealed *Streptococcus haemolyticus* in the blood, and the same organism along with *Staphylococcus aureus* in the lungs and pleural exudate.

Microscopical sections of the skin from a number of parts showed that where the surface was denuded of epithelium the cutis was densely infiltrated by polymorph leucocytes. In parts with intact epithelium there was no inflammation and the skin glands, hair follicles and elastic tissue appeared normal.

The consolidated areas in both lungs proved to be septic infarcts. Some of those in the right lung had proceeded to abscess formation. Arteries related to these areas contained thrombi, which may have been of embolic origin from the tricuspid valve. Both kidneys

had calcified casts in the collecting tubules, and showed the typical picture of medullary nephrocalcinosis at an early stage.

The findings in this case were so similar to those of his elder brother (Case 2) that the diagnosis of skin sepsis made in the latter was revised to that of epidermolysis bullosa hereditaria letalis. The family details are depicted in Fig. A.

FIG. A.

Case 4. M.C., a girl, was the first child of healthy, unrelated parents born at term in an Edinburgh nursing home after a healthy pregnancy on July 13, 1948. Small white spots on the tongue and an inflamed area on the roof of the mouth were noted shortly after birth. Subsequently blisters appeared on the hands, feet, and buttocks. She was admitted to the Royal Hospital for Sick Children, Edinburgh, on July 19 aged 6 days.

On examination, she was well nourished and adequately hydrated. There were bullous lesions on the fingers, toes, trunk, and also on the buccal musosa. The contents of the lesions were clear or occasionally haemorrhagic and no growth was obtained on culture. There was no leucocytosis. The maternal Wassermann test was negative.

The child fed well but did not gain weight. She was afebrile but fresh lesions appeared on the hands, feet and trunk. Treatment, none of which was effective, consisted of several local applications including gentian violet, and sulphonamide creams and also systemic penicillin and sulphonamide. Finally after a diagnosis of epidermolysis bullosa had been suggested the parents requested her discharge on August 30 and she died a few days after her return home. There was no necropsy.

Case 5. D.C., a boy, was the third child of the parents of Case 4 and was born spontaneously at full term in an East Lothian hospital. Blisters were noted at birth, and when he was seen as an out-patient in Edinburgh two days later bullae were present on the right thumb, scrotum, thighs and upper alveolar margins. A diagnosis of pemphigus neonatorum was made and penicillin therapy instituted. A culture of the bullous fluid grew *Staphylococcus albus* and a non-haemolytic streptococcus.

The child's subsequent progress was stormy, for slight trauma such as a hard rubber teat or firm handling produced bullae. Lesions occurred over the buttocks, in the axillae, and on the extremities. The bullae contained serous or sometimes haemorrhagic fluid.

When he was seen in June, 1953, at the age of 2 years 4 months, the child was well developed mentally and physically. He had thin atrophic scars on the hands, feet, over the knees, and near the axillae. Small epidermal cysts were to be seen in the scars. He had an unruptured haemorrhagic bulla at the base of the left thumb. The left thumb-nail was thickened. He had no defects of hair or teeth.

TABLE
BULLIOUS ERUPTIONS IN THE NEWBORN

Disease or Condition	Aetiology	Character of Lesions	Distribution	Mucosal Involvement	Other Ectodermal Defects	Scarring	Response to Drugs	Course
Epidermolysis bullosa	Congenital skin defect	Clear blisters; sometimes haemorrhagic non-inflammatory base	Sites of trauma or friction	Yes	Yes	Yes or no	Nil	Chronic or fatal
Bullous impetigo	Staphylococcal	Blisters, clear, opaque, purulent	General, particularly flexures	Possible	No	Yes	Antibacterial drugs	Short
Congenital syphilis	<i>Trep. pallida</i>	Bullae and maculopapules	Palms, soles, trunk and limbs	Yes	Yes	No (other than rhagades)	Antiluetic	Short
Dermatitis herpetiformis	?	Vesicles and bullae in crops, also urticarial lesions	In infants face and limbs chiefly involved	Sometimes	No	Minimal in long-standing cases	Arsenic and sulphones	One-third curable. Chronic or recurrent
Burns	Hot bottles	Erythema, bullae, desquamation	Anywhere	No	No	Yes if deep	—	Depends on type, depth, and therapy
Congenital porphyria	Hereditary metabolic disorder	Red urine, photo-sensitivity of skin, erythema, bullae	Areas exposed to sunlight	No	Pigmented teeth	Pigmented scars	Nil	Chronic
Erythema multiforme bullosa	Allergy ?	Dusky red circinate plaques, papules, bullae	Trunk, limbs, face	Yes	No	No	Topical only	Short or recurrent
Dermatitis medicamentosa	Drug allergy: iodides, bromides, phenolphthalein	May be vesicular	No particular site	No	No	No	Topical only	Short
Papular urticaria	Allergy	Papules, bullae, or limbs	Trunk only or limbs	No	No	No	? Anti-histamines	Short or recurrent
Chickenpox	Virus	Vesicles, pustules	Trunk, face, limbs	Yes	No	Yes	Nil	Short
Smallpox	Virus	Vesicles, pustules	Limbs, trunk, face	Yes	No	Yes	Nil	Short
Kaposi's varicelliform eruption	Virus	Vesicles, pustules	Exposed parts	No	Pre-existing skin disease of infantile eczema or Besnier's prurigo	No	Antibacterial drugs for secondary infections	May be fatal
Herpes zoster	Virus	Vesicles	Classical girdle	No	No	Yes	Nil	Short
Bullous erysipelas	Group A haemolytic streptococci	Raised tender erythema, bullae	Peri-umbilical, limbs, face, trunk	Rarely	Nil	Nil	Antibacterial drugs	Short with therapy
Benign familial pemphigus (Hailey's disease)	Familial	Vesicles and bullae	Anywhere	No	No	Nil	Possibly sulpha drugs and antibiotics	Benign chronic
Contact dermatitis	Allergy	Often vesicles and bullae	Anywhere	No	No	No	Removal of sensitizing agent	Short
Phytophotodermatitis	Occurs when skin sensitized by contact with certain plants is exposed to sunlight	Vesicles and bullae	Areas exposed to sunlight	No	No	No	Nil	Short
Acrodermatitis enteropathica	May be vitamin deficiency or bowel infection	Crops scaling, vesiculobullous	Near orifices, around eyes, elbows, knees, hands, feet	Yes	Hair scanty	No	? Diodoquin	May be fatal

Pemphigus vulgaris is never seen in infancy or early childhood

In epidermolysis bullosa, the bullae occur at the points of trauma or of pressure. The usual sites of lesions in the baby are the toes, heels, buttocks, scapular regions, axillae, elbows, fingers, ears and occiput. In older children, the hands and fingers, elbows, knees and toes are more often affected. The contents of the bullae may be serous or haemorrhagic and are sterile on culture. The fingers and toe-nails are frequently thickened and deformed or may be absent. The diagnosis is based on the finding of these features. Nikolsky's sign—the ready detachment of the horny layer of the skin by trauma—mentioned by some as a valuable diagnostic aid, may not be present, but in any case it is found in other bullous skin diseases.

There are several theories on the aetiology of the disease but none has been accepted universally. These include endocrine upset, increased irritability of the cutaneous vascular system, congenital neuro-vascular anomaly and sympathicotonia, but it is now widely accepted that there is some inherited disturbance of the skin structure. Several workers have suggested that it is due to an absence or deficiency of elastic fibres in the papillary and sub-papillary layers of the skin. Kanoky and Sutton (1910) stated that this deficiency was general and that it was not confined to the affected areas. Excess urinary porphyrins were found in some cases (Turner and Obermayer, 1938) but it is probable that these were really examples of congenital porphyria. A German article (Langhof, 1952) postulated an upset in hyaluronidase metabolism, due to a deficiency in a serum heparin-like substance. The latest paper (McDaniel, 1954), recording a severe dystrophic variety with recessive inheritance, described complete absence of elastic tissue in the upper half of the dermis.

Males are affected more frequently than females and the disorder is found in all races. The onset may be at birth or shortly after but in the less severe types the lesions may not appear for months or even years.

The pathology of the rapidly fatal form has been described in several papers. Herlitz (1935) mentioned that the skin was thinner than usual with degenerated elastic fibres and rudimentary hair follicles and sweat glands. Lamb and Halpert (1947) stated that the corium was loose, fibrillar and relatively acellular, but they mentioned that normal collagenous bundles, hair follicles, sebaceous and sweat glands were present. Normal skin glands were mentioned by Schäffer (1951) but he found a thin epidermal layer, and, while the amount of elastic tissue was reduced, the elastic filaments were not entirely atrophied. Matheson and Rosner (1949)

considered that there was deficient elastic tissue in the superficial layers of the skin. In the two fatal cases in our series which were studied in detail, no abnormality of the histological structure of the skin was found. In Case 3, secondary infection obscured any clinical features of nephrocalcinosis that might have been present and also the picture at necropsy.

The two main types of the condition have been mentioned previously. The simple variety produces lesions which heal in from two to 10 days, leaving no scar. The mucous membrane is involved in very few patients. Most of those with this type of epidermolysis improve at puberty.

The dystrophic variety has been subdivided into three (Cockayne, 1933). The first type, which is inherited as a dominant trait, does not interfere with growth or development. The lesions may be severe over the hands or toes and over other points liable to trauma or pressure. Finger- and toe-nails may be lost and on re-growth are frequently thickened or deformed. The scars, which result on healing, are thin and atrophic and may contain small epidermal cysts. Puberty may produce improvement or else the abnormal traumatic response may persist throughout life. Cases 4 to 6 were of this group and the fact that the trait is inherited as a dominant is shown by the family trees (Fig. B and C). These reveal that the condition is transmitted by affected members of either sex. Another feature is that the sex ratio is equal in both these families. Case 4 shows that the prognosis must be guarded although secondary infection may have been responsible for this fatality. Her brother (Case 5) who survives, presented a difficult nursing problem. He had to be wrapped in cotton wool to prevent the formation of extensive bullae. Handling had to be reduced to a minimum and required great care. Even feeding was a problem as a rubber teat, unless softened by repeated boiling, blistered the child's mouth and gums.

The second type seems to be inherited as a recessive and in many cases the children are undersized and below normal intelligence. The teeth may be more liable to caries and the mucous membranes of the alimentary and respiratory tracts are frequently affected. Few survive to maturity.

Cockayne's third variety contains miscellaneous conditions showing features of both epidermolysis and congenital ectodermal dysplasia.

The form described by Herlitz (1935), which he called epidermolysis bullosa hereditaria letalis, shows the following features: (1) It begins at birth or soon after. (2) Death usually occurs before the third month of life. (3) There is marked deformity of the finger- and toe-nails or some of these nails

may be missing. (4) The bullae of the skin or mucous membranes may be haemorrhagic. (5) Nikolsky's sign may be present but the production of blisters by experimental trauma is unsuccessful. (6) Healing takes place without scarring. (7) The inheritance is recessive. In some cases no history of the condition exists previously, in others the parents were first cousins and more than one case may occur among siblings. (8) There are congenital skin defects such as a thin corium, a reduction in the number of sweat glands and hair follicles. The elastic tissue is diminished. (9) Skeletal atrophy may occur near areas of skin showing localized congenital defects.

Since Herlitz's paper other examples of this fatal form have been described (Davidson, 1940; Brandberg, 1941; Schroder and Wells, 1945; Black, Wilhelm, Gilbert and White, 1945; Lamb and Halpert, 1947; Matheson and Rosner, 1949; Schäffer, 1951; Kagen, Williams, Giffen and Wiley, 1952; and Leland and Hirschl, 1954). The paper by Leland and Hirschl stated that before their own paper, which added two further examples, 32 patients with epidermolysis bullosa hereditaria letalis had been reported in the world literature but clinical features as well as the pathology have differed from the details given by Herlitz. For instance, one of the patients recorded by Kagen *et al.* (1952) lived for 16 months.

In the present series Cases 1 to 3 were considered to represent the condition of epidermolysis bullosa hereditaria letalis. Most of the features stipulated by Herlitz were present although bone atrophy did not occur and it was difficult to decide whether lesions healed without scarring in Cases 2 and 3 because of their early deaths.

The parents of the brothers (Cases 2 and 3) were first cousins, a feature in two of the three families studied by Herlitz. Case 1 was born of unrelated parents and there was no known history of bullous conditions in previous generations.

One surviving sister of Cases 2 and 3 is subject to grand mal type epilepsy. Another child died of multiple congenital anomalies a few hours after birth.

The prognosis in epidermolysis bullosa must depend on the type. In the simple varieties it is excellent, and the condition should improve about puberty in most cases. In the dystrophic forms it can be more serious, and Cockayne mentioned a recessively inherited fatal variety which may have included cases similar to those described by Herlitz. In epidermolysis bullosa hereditaria letalis, death occurs almost invariably within three months of birth.

The common dystrophic type (Cases 4 to 6) may have serious consequences, as in the baby in Case 4 who died of blistering with sepsis in early infancy. Secondary infection and difficulties in management are the two dangers. Cases 5 and 6, while both are liable to severe blistering, are normal, lively youngsters who do not allow their skin disability to interfere with their activity.

No effective treatment has been found although in a recent article Langhof (1952) claimed to be able to prevent blistering using an ointment containing heparin. He claimed protein shock therapy was also effective. He postulated a disturbance in hyaluronidase metabolism and a deficiency of heparin or a heparin-like substance in the tissue fluid. He stated that hyaluronidase, if administered, increased the number and size of bullae in a case of epidermolysis. Supplies of the heparin ointment 'thrombophob' were obtained from Germany and administered to Cases 5 and 6. It was rubbed into the hands and knees three times daily but in neither case was blistering prevented although one mother thought that the blisters were not so big. This mother, however, felt that equally good, if not better, results were obtained using an antihistamine locally and parenterally.

As one cannot cure or control the condition, the aims of therapy must be (1) to handle carefully so as to prevent bullae forming; (2) to limit the spread of established bullae; (3) to prevent secondary infection and hasten healing.

In the baby, the first aim can be served by a thick wrapping of cotton wool, and infrequent and careful handling. In the older child, however, it is almost impossible to prevent trauma in an active and otherwise healthy child.

The second aim is easily executed. Blisters should be snipped as soon as they appear and the contents expressed.

The third point does not seem such a problem in the older child as in infancy; cleansing the skin with 1% cetrimide, and the application of a sterile, non-boric-containing talc preparation is recommended in babies, but in older children a drying paste should be applied. The mother of one of our cases, a doctor's wife, has, after many trials, found Lassar's paste to be the most effective. Infection, particularly in babies, should be countered by adequate systemic antibiotic therapy as well as by local applications.

As might be expected in a disease of unknown aetiology, corticotrophin (A.C.T.H.) and cortisone have been tried but without benefit (Lever, 1951; Jensen, 1951; Cannon, Hopkins, Andrews, Colfer,

Gross, Nelson and Howell, 1951; Leland and Hirschl, 1954).

Summary

Six cases are recorded of epidermolysis bullosa in infants. Three of them were the rare recessive form known as Herlitz disease; the other three were the dominant dystrophic variety.

The aetiology, pathology, clinical features and methods of treatment of the disease are discussed, and a table is given of the points for differential diagnosis of bullous eruptions in the newborn.

All cases of the Herlitz type and one of the others died. No abnormality of skin structure was found in the two cases of Herlitz disease which were examined after death.

We wish to thank Professor R. W. B. Ellis, Dr. Margaret B. Martin and Dr. D. N. Nicholson for permission to publish these cases, and Dr. A. R. Macgregor and Dr. A. D. Bain for the detailed post-mortem reports and special dermatological studies. We are indebted to T. C. Dodds, D. Hill and D. Campbell for cutting many thousands of skin sections. Finally we are most grateful to Professor R. W. B. Ellis, Dr. G. A. Grant Peterkin and Dr. Margaret B. Martin for their

help and their constructive criticism in the preparation of this paper.

The 'thrombophob' cream was provided for clinical trials by Nordmark—Werke—G.m.b.H., Hamburg, Germany.

REFERENCES

- Black, R. A., Wilhelm, E., Gilbert, C. S. and White, C. J. (1945). *J. Amer. Med. Ass.*, **129**, 734.
 Brandberg, O. (1941). *Ann. paediat., Basel*, **157**, 162.
 Cannon, A. B., Hopkins, J. G., Andrews, G. C., Colfer, H. F., Gross, P., Nelson, C. T. and Howell, C. M., Jr. (1951). *J. Amer. med. Ass.*, **145**, 201.
 Cockayne, E. A. (1933). *Inherited Abnormalities of the Skin and its Appendages*, p. 118 *et seq.* London.
 Davidson, L. T. (1940). *Amer. J. Dis. Child.*, **59**, 371.
 Hailey, H. (1953). *Sth. med. J., Bgham, Ala.*, **46**, 763.
 Herlitz, G. (1935). *Acta paediat., Uppsala*, **17**, 315.
 Jensen, C. (1951). *Ugeskr. Læg.*, **113**, 605.
 Kagen, M. S., Williams, L., Giffin, W. and Wiley, R. (1952). *Wis. med. J.*, **51**, 766.
 Kanoky, J. P. and Sutton, R. L. (1910). *J. Amer. med. Ass.*, **54**, 1137.
 Lamb, J. H. and Halpert, B. (1947). *Arch. Derm. Syph., Chicago*, **55**, 369.
 Langhof, H. (1952). *Derm. Wschr.*, **126**, 764.
 Leland, L. S. and Hirschl, D. (1954). *Amer. J. Dis. Child.*, **87**, 321.
 Lever, W. F. (1951). Discussion of paper by Zeligman, I. and Robinson, H. M. *Arch. Derm. Syph., Chicago*, **63**, 669.
 Matheson, A. and Rosner, D. C. (1949). *Amer. J. Dis. Child.*, **78**, 708.
 McDaniel, W. H. (1954). *Archives of Disease in Childhood*, **29**, 334.
 Schäffer, G. (1951). *Acta derm.-venereol., Stockh.*, **31**, 704.
 Schroder, C. H. and Wells, A. H. (1945). *Minn. Med.*, **28**, 128.
 Turner, W. J. and Obermayer, M. E. (1938). *Arch. Derm. Syph., Chicago*, **37**, 549.