REVIEW

EPIDERMOLYSIS BULLOSA HEREDITARIA

(A brief review with a study of coagulation defects and Case reports)

By

M. P. MATHUR, M. B; B S; F. D. S. (London),

S. K. MATHUR, M. B; B. S.

and

H. C. SAXENA, M B; B. S.

Department of Dermatology & Venereology, S.M S. Medical College, Jaipur.

Epidermolysis bullosa hereditaria is an interesting disease of skin in which vesicles or bullae are produced by friction or slight traumatism. The condition is comparatively a rare entity with a strong hereditary bias. Goldscheider was the first who brought the condition in light. Broadly speaking there are two types of this condition namely:—

1) Simple.
2) Dystrophic.

In both the forms bullae are produced after irritation or trauma. In women these are more marked just before the onset of menstrual flow and less after it has begun. The severity of this condition is diminished during the period of pregnancy.

CLASSIFICATION

Roger's et al have classified the epidermolysis bullosa group of diseases as under :—

		Disease	Transmission.
I)	Non Scarring Types.	1. Epidermolysis bullosa Simplex.	Dominant.
		2. Recurrent bullous eruptions of the hands and feet.	Dominant.
		3. Epidermolysis bullosa hereditaria letalis.	Recessive.
		4. Atypical cases.	Variable.
II)	Scarring Type.	1. Epidermolysis bullosa dystrophica.	Recessive
		2. Epidermolysis bullosa dystrophica.	Dominant
		3. Acquired Epidermolysis bullosa dystrophica.	Uncertain.
		4. Cutaneous porphyria	Variable.

III) Few special varieties of Epidermolysis Bullosa have also been described.

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1. *Guy's Type* :—Hair of scalp and eyebrows fall out. Bullae appear after the age of a few years and heal without scar.

2. *Wende's Type* :—Complete baldness with bullae about the orifices.

3. *Heinrichsbauer's Type* :—Bullae associated with large areas of dark bluishred skin, on all the four extremities.

4. *Macular Type* :—Pemphigoid eruption with diffuse brown pigmentation of skin. Dwarfism, microcephaly, acrocyanosis and lack of hair are further features.

5. *Pasini's atrophic & Albopapuloid Type* :—Here bullae and few white firm elevated lesions are formed.

AETIOLOGY

The disorder is often hereditary and familial. Its occurence can be traced through several generations. Various theories have been propounded to explain the aetiology but the most satisfying one is as follows:—

1. Hyaluronidase enzyme system is adversly affected in these cases. Hyaluronidase has been found of being present in the skin of patients with the Epidermolysis Bullosa. Its ability to depolymerise the hyaluronic acid "cement" of capillary walls might account for the capillary fragility and exudation of fluid with subsequent bullae formation. To evaluate the possible influence of hyaluronidase further, an inhibitor of hyaluronidase (Phosphorylated hesperidine) was given to few patients and clinical improvement was noted.

PATHOGENESIS

Vesicular changes within the basal cells is the first step in the blister formation. In a small proportion of cases there is fragmentation or disappearance of elastic tissue of corium A lack of adhesion between epidermis and corium with serous exudation is present in all the cases. Bullae do not contain epithelial cells (Compare pemphigus.)

CLINICAL FEATURES

1. *Simple type* :—In this form the bullae appear on any part of the body exposed to friction or injury. The lesions are filled with clear serum. They are painless and do not itch. When the lesions heal up, only temporary pigmentation is seen which fades away after the lapse of a few days. This is because of the fact that the bullae are chiefly formed in stratum corneum. Mucous membranes are not involved in this form. The lesions start appearing shortly after bath. The other appendages of skin e.g. nails, teeth and hair do not show any abnormality. The inheritance is by a simple dominant character.

Nikolsky's sign is positive.

2. *Dystrophic Type* :—In this variety lesions occur on extremities mostly over hands, feet, elbows and Knees. The bullae may contain hemorrhagic fluid. Scarring is common and pigmentation permanent. A group of milia is often seen on the dorsal surface of hands and forearm. Nails show dystrophic changes and

may actually be destroyed. Mucous membranes of mouth and tongue may show bullae, infiltrated areas or patches of leukoplakia. The inheritance may be dominant or recessive.

COURSE AND PROGNOSIS

Because the disease is inherited so the natural course persists throughout life. In simple type there is tendency to clear up by puberty and life expectency is normal. In dystrophic type the scarring results in marked deformity, This condition is usually fatal.

DIFFERENTIAL DIAGNOSIS

4. *Bullous Impetigo Contagiosa*:—This inflammatory condition usually appears few days after the birth with bullae anywhere on the body except palms and soles. Response to antibiotics is good.

2. *Bullous Syphiloderma*:—Palms and soles are always involved. Lesions heal without scarring except rhagades. Other syphilitic stigmata are usually present.

3. *Incontinentia Pigmenti.*:—Lesions are smaller in size, thick walled and are resistent to compression and palpation in contrast to Epidermolysis bullosa. Further they are arranged linearly and content is thick yellow.

4. *Ritter's Disease*:—It starts in the first few weeks of extra uterine life, lesions appear first on the face, chin and then spread to whole body. There is no exfoliation and mortality is high.

5. *Pemphtgous Erythematosus*:—Evolution of symptoms is slower. Mucosa is more frequently involved. Extremities are spared of lesions.

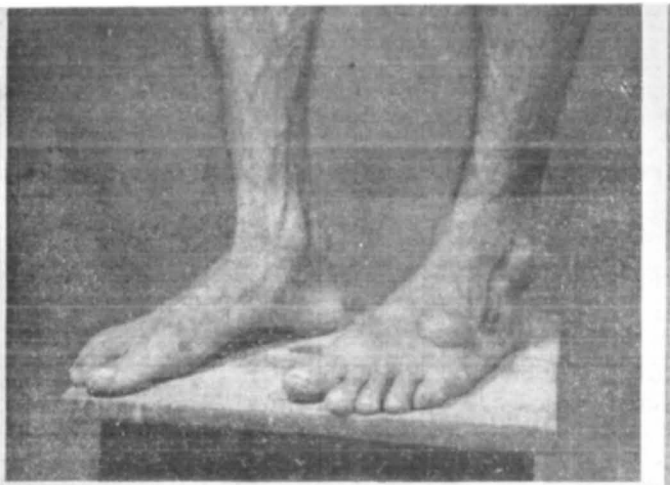
COAGULATION DEFECTS IN THESE PATIENTS

According to the studies of P. J. Waardenbergh and H. J. Vermeulen, the patients with epidermolysis bullosa exhibit a coagulation paradox. In this the patients of the above disease and some of their relatives show a shortened coagulation time and along with this, these patients reveal a resistance to anticoagulant effect of I. V. heparin with an unusual sensitivity to heparin in vitro. The healthy relatives who also show these coagulation defects especially the heparin resistance represent the heterozygous intermediate state. The test is done as follows:

Heparin Tolerance Test:—It is done in vivo by measuring the clotting time, 30, 60, 90, 120 and 150 minutes after the intravenous injection of 50 mg. of heparin by Lee and White and glass capillary method. Further the plasma is subjected to an in vitro tolerance test by the addition of 6 mcg. of heparin to the plasma collected at each of above time intervals. By the addition of heparin to the plasma, in vitro, causes paradoxically a lengthening of clotting time.

It has been found that hyaluronidase accelerates the clotting in small amounts and retards in large amount in vitro. In vivo a shortening of coagulation time was noted when hyaluronidase was injected I. V. into the normal persons.

Photo 1



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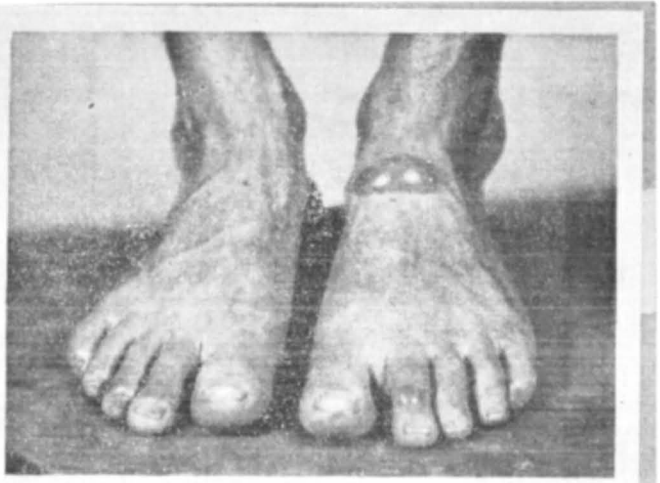

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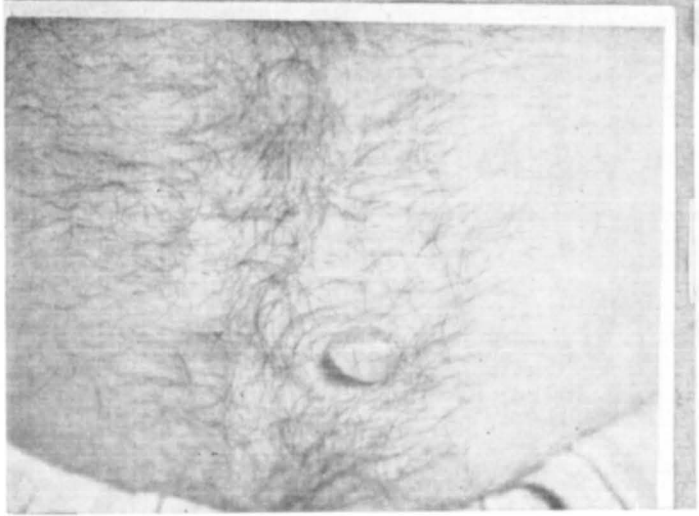

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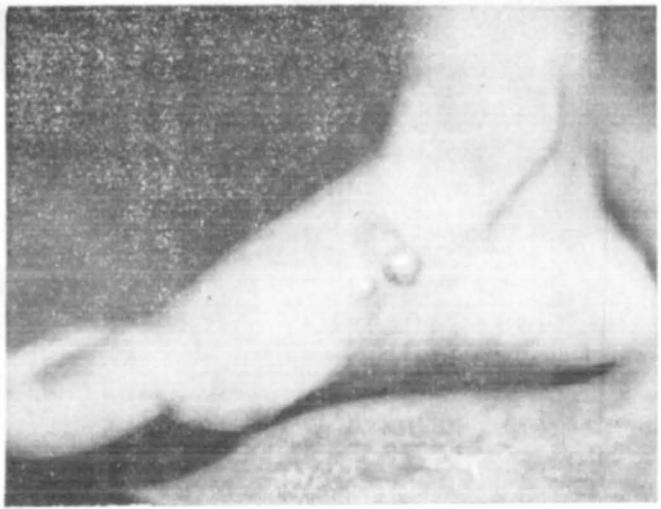


1, 2, 3. Bullae seen over the feet and abdomen of Case No. 1. 4. Bullae seen over the feet of Case No. 2.

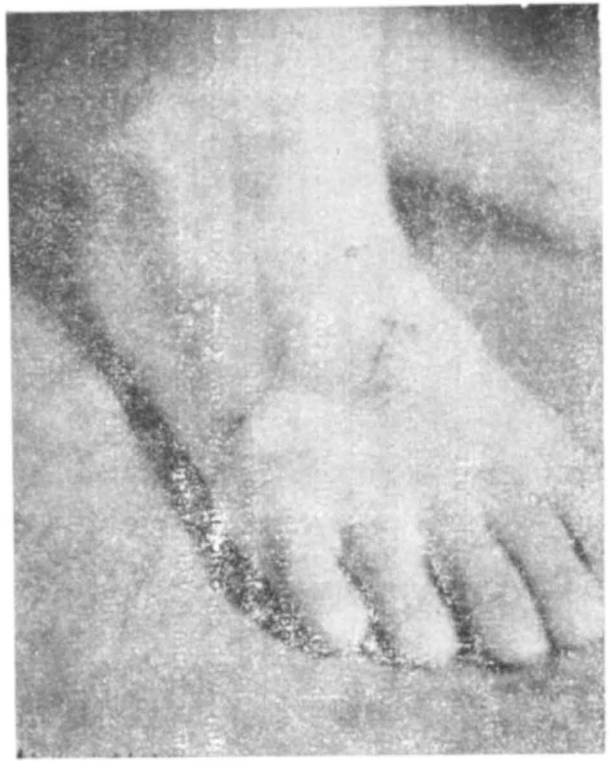


Photo 5.
Bullae seen over the feet of Case No. 2.

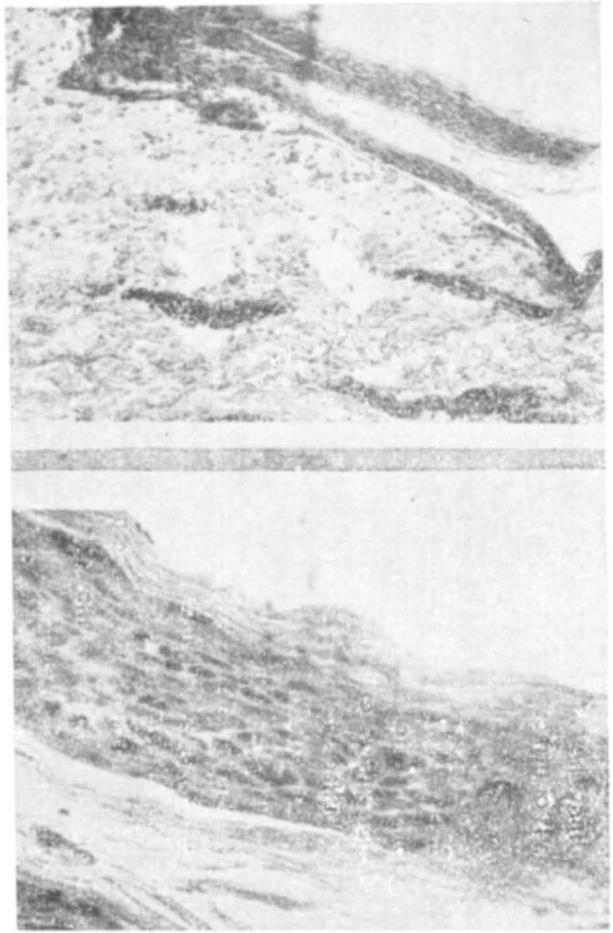


Photo 6

Photo 7

Photomicrographs of histopathoiogical section of skin from a bullae showing an increased space between epidermis and dermis (Case No. 1)

TREATMENT

No satisfactory treatment is found as yet. Pressure bandages are helpful locally. Antibiotics are given for secondary infections. Cortico-steroids are reported to limit the extension of the lesions. Frophylaxis of parts by protecting from trauma is of utmost importance.

CASE REPORTS

1. P. S.—A 24 years Hindu male, whose mother, grandmother and a few other relations had the same type of disease, came to our outpatient department for recurrent bullous eruptions over the body since birth. His parents had noticed these bullae when they started handling him after his birth. The lesions have been appearing regularly since then. Upto the age of sixteen he had been getting these bullae following very trivial trauma. But after that, appearance of lesions preceded a more severe friction and irritation. Winters are tolerated better, while rainy season is worst as regards the frequency of the lesions. The patient had been exeriencing excessive sweating of the face, palms and soles and axillae since birth. Palms and soles actually become so wet with the sweat that even small drops can be seen falling down.

The common incidence following which he develops bullae are riding on a camal, prolonged cycling, tying a belt around the waist and on wearing tight shoes.

Clinical Findings:—On physical examination a healthy and well developed young man of normal intelligence was found to have bullous eruptions of varying size and shape over his both legs, feet, and abdomen. Bullae contained clear serous fluid. They were painless and without itching. No scarring was seen after their subsidence. The hair was in normal intensity and colour. Teeth were normal. No lesions were seen on the mucous membranes. Nails were absolutely normal. No milia were found. Nikolsky's sign was positive. Examination of internal systems revealed nothing abnormal.

Laboratory Studies:—A White cell count of 6100/cu.mm. & Normal hemoglobin level and a differential count was found, E. S. R. was 12 mm for first hour. Blood V. D. R. L. was negative.

Stool and urine were normal.

Screening chest- N. A. D. in both heart and lungs.

Examination of fluid from bullae showed the presence of a few WBC of which polymorphs were predominating.

Histopathological Observations:—There was moderately severe infiltration of upper corium with chronic inflammatory cells. A clear space was seen between epidermis and corium. With Verhoff's stain, there was absence of elastic tissue in upper corium.

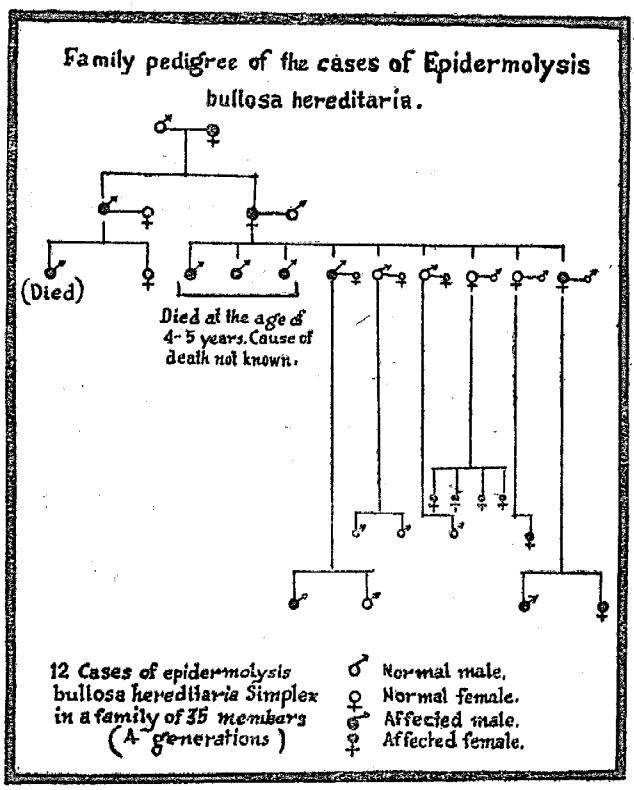
2. *L. S.*:—A child of $4\frac{1}{2}$ years had been getting bullous eruptions over his limbs following friction. Trouble started just after birth. On examination bullae were found painless and contained clear fluid. There was no sepsis and lesions healed up without any scarring.

3. *M. K.* :—60 years hindu female came with the same type of trouble. She had also started getting the bullous eruptions just after birth. Bullae never appeared on the mucous memberane. The intensity of the lesions had been more marked just before the onset of each menstrual flow.

The coagulation defects studied by us showed the following results :—

Case No.	Coagulation Time by glass capillary method.	Coagulation Time by Lee & White method.	Coagulation time after I. V. heparin		
			After 30 min.	After 60 min.	After 90 min.
Normal	7 min. 30 sec.	6 min. 30 sec.	15 min.	12 min. 30 sec.	10 min.
No. 1. (p. s.)	3 min. 30 sec.	6 min. 51 sec.	22 min.	30 min.	18 min.
No. 2. (L. S.)	3 min. 45 sec.	Not done	Not done	Not done	Not done.
No. 3. (M. K.)	2 min. 40 sec.	3 min. 45 sec.	24 min.	30 min.	14 min.
No. 4. (S. S.)	3 min. 45 sec.	5 min. 30 sec.	25 min.	15 min.	15 min.
No. 5. (D. S)	3 min. 30 sec.	Not done	Not done	Not done	Not done.

FAMILY PEDIGREE OF THE CASES OF EPIDERMOLYSIS BULLOSA HEREDITARIA.



The reference from above mentioned observations reveals deminished coagulation time in Case No. 3. No tolerence to I. V. heparin was found these cases. The in vitro heparin test was not performed. Case No. 4 & 5 did not allow I. V. injection so the subsequent observations were not made.

COMMENTS.

Twelve cases of Epidermolysis Bullosa were found in a family of 35 members of 4 generations. Out of these three cases came under direct observation. Becasue of the absence of scarring, haemorrhagic bullae and the involvement of mucous memberanes the cases were labelled as Epidermolysis Bullosa Simplex. No milia like bodies which are generally seen in the dystrophic variety were found in our cases. Nikolsky's sign was positive in all the three cases. The study of coagulation defects revealed a shortened coagulation time of case No. 3 (M. K.) The heparin tolerence test was negative in all the three cases studied. The patient with simplex variety could live up to normal age as is evidenced by the age of case No. 2 who is 60 years old at present.

SUMMARY.

A short review of the rare skin malady Epidermolysis Bullosa hereditaria has been made. Three cases of Simplex variety are reported. The inheritence seems to be of Mendelian Dominant type. In the family history, nine more members were found to be affected with this disease. The results of studies of coagulation defects were not consistent with those reported by Waardenbergh & Vermeulen.

ACKNOWLEDGEMENT

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