Acta Dermatovener (Stockholm) 53: 53–60, 1973

EPIDERMOLYSIS BULLOSA DYSTROPHICA DOMINANS IN TWO FAMILIES IN THE FAROE ISLANDS

A Clinico-genetic Study of 56 Living Individuals

Høgni Debes Joensen

From the Faroe Islands

Abstract. Two families in the Faroe Islands in which the occurrence of a bullous skin disease was observed were examined concerning the clinical course of the disease and its hereditary transmission. It was found that a total of 73 individuals had been affected; fifty-six of these were still alive. The disease would make its first appearance during early childhood and was manifest in a tendency to develop bullae of the skin after moderate, mechanical traumata. The bullae left scars and milia; occasionally, bullae of the mucous membranes might develop. Malformation of nails was in evidence in almost all cases and, in one of the families, local absence of skin on the feet might be a congenital phenomenon. The disease appeared to be systematically transmitted by a dominant autosomal gene. Thus, the pathological picture observed in both families is compatible with that of epidermolysis bullosa dystrophica dominans (EBDD).

In 1886, Köbner (5) applied the term epidermolysis bullosa hereditaria (EBH) to the disease.

T. Gedde-Dahl, Jr (4) has recently set up the classification shown in Table I according to which three subtypes of epidermolysis bullosa dystrophica dominans (EBDD) may be differentiated.

EBDD (Cockayne-Touraine) comprises a heterogeneous group of dominant, dystrophic EB, but with absence of demonstrable albupapuloid elements (9).

EBDD albopapuloidea (Pasini) is a type of EBDD in which several minor albopapuloid papules, or papules reminiscent of urticaria, develop spontaneously, i.e. they are not preceded by the formation of bullae; they are localized to the trunk of the body and develop during, or immediately before, adolescence (8, 9).

EBDD (Bart) includes symptoms such as local absence of skin on the lower extremities, a formation of bullae on skin and/or on mucous membranes, as well as malformation of nails and/or anonychia. The disease is hereditary, being transmitted by a dominant gene; penetration is complete, but expressivity may vary (1, 3).

In 1970, the School Medical Officer in Tórshavn called the author's attention to a skin disease which he had observed in individuals in his district. The disease was manifest in two pairs of siblings who were related and whose parents supplied the information that the disease was a well-known and common affection in the family concerned.

A more detailed investigation revealed that quite a number of the members of this family were affected and, in addition, contact was established with another, equally large, family in which a similar disease was observed.

As it seems rather remarkable that the incidence of an otherwise rare disease could establish such a hold in a small country like the Faroe Islands, numbering a mere 40 000 inhabitants, and also because it is the first collective study of epidermolysis bullosa in the Faroe Islands, it was deemed justified to have the present report published.

MATERIAL AND METHODS

The series comprises two families in which 37 and 36 members, respectively, were affected. Both families are natives of the largest of the Faroe Islands, Streymoy. Data were collected during the period from June 1970 to June 1971. The genealogical trees of both families are constructed on the basis of information obtained by the author from numerous affected as well as non-affected members of these families.

Thorough studies revealed that the earliest ancestors

Table I. *Classification of hereditary epidermolysis bullosa*

	Nail dystrophy	Scarring	Clinical hallmarks	Postulated gene loci
Autosomal dominant				
EB simplex (Weber–Cockayne)	−	−	Feet or feet and hands	Koebner–Weber–Cockayne locus (multiple alleles)?
			↕	↕ ?
EB simplex (Koebner)	−	−	Generalized blistering	
EB simplex (Ogna)	−/+	−	Bruising skin + blistering	Ogna locus
EB dystrophica (Cockayne–Touraine)	+/−	+/−	Heterogeneous. Majority with congenital, localized EBD	Cockayne–Touraine locus? ↕ ?
EB dystrophica albopapuloidea (Pasini)	+	+	Congenital, localized EBD Pasini papules	Pasini locus
EB dystrophica (Bart)	+/−	+/−	Congenital, localized absence of skin + inconstant blisters.	Bart locus
Autosomal recessive				
EB dystrophica (Hallopeau–Siemens–Herlitz)	+	+	Congenital, localized, nonlethal	Hallopeau–Siemens–Herlitz locus (multiple alleles)
			↕	↑
Or	+	−/+	Lethal	↓
EB dystrophica polydysplastica	+	+	Congenital, generalized, sublethal, mutilating	?
			↕	↓
	+	−/+	Inverse	
EB dystrophica neurotrophica	+	+	Hypacusis + "semitardive", localized EBD	A gene complex?
EB dystrophica ulcero-vegetans	+	+	Heterogeneous	?
Others				?

in the two families were kindred; the ancestor of family A (no. 1) was found to be a descendant in the sixth generation of the same man of whom the ancestor of family B (no. 1) is the descendant in the fourth generation.

The probands in family B are nos. 34, 35, 36, and 37. It was by mere chance that the author learned about family A, namely when some of the affected members of family B, nos. 20 and 21, told that they knew others, nos. 27 and 28 in family A, who were suffering from a disease similar to their own. The author contacted those upon whom this family A was charted. The probands are marked by →.

Affected subjects, as many as possible, were interviewed and examined by the author. Examination included inspection of nails, of affected skin areas, and of scars and milia, if any. The trunk of the body was not systematically examined and a search for Pasini-papules was not made because the author did not realize the significance of the latter until the investigation had been concluded.

Table II is elaborated on the basis of replies received from affected subjects who were asked to tell about their disease; the questions were embodied in questionnaires of uniform type which had been prepared in advance; answers to the questionnaires were obtained in all cases; in the case of children or deceased subjects, the answers were supplied by parents or relatives.

As it proved impossible to establish personal contact with people who had emigrated to other countries (Denmark and Greenland), data were obtained either via correspondence or from the parents of these concerned.

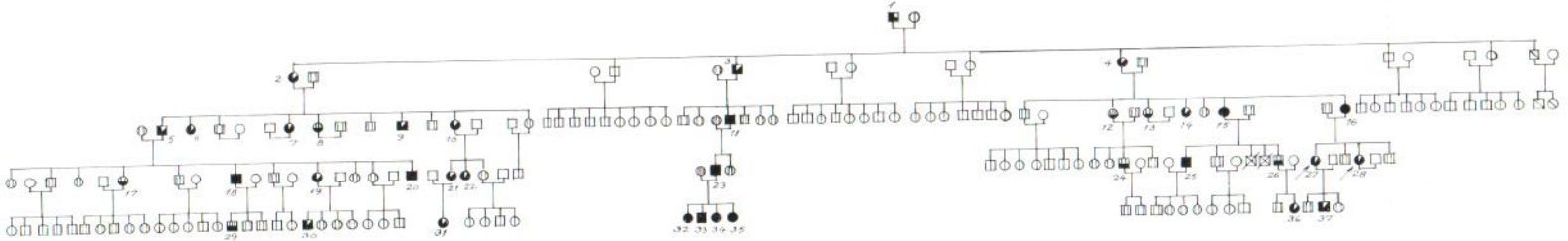
Among the affected members of family A, 14 were examined by the author (nos. 8, 11, 12, 15, 16, 18, 20, 23, 25, 29, 32, 33, 34 and 35) and replies by letter were obtained from another 14 (nos. 7, 13, 17, 19, 21, 22, 24, 26, 27, 28, 30, 31, 36, and 37). Among members of family B, 21 were examined by the author (nos. 8, 11, 12, 13, 15, 17, 18, 20, 21, 22, 23, 24, 27, 28, 31, 32, 33, 34, 35, 36, and 37) and replies by letter were received from 7 (nos. 14, 16, 19, 25, 26, 29, and 30).

All other members of these families of whom it was known that they had been affected had died before the investigation was commenced and hence, data on these cases had to be obtained from their siblings or descendants.

CLINICAL DATA

The number of affected individuals in total and the number of affected survivors are recorded in Table II. In family B, formation of bullae was in evidence in all of the affected members while this tendency was absent in 8 of the affected members of family A; malformation of the nails

Fam. A.



Fam. B.

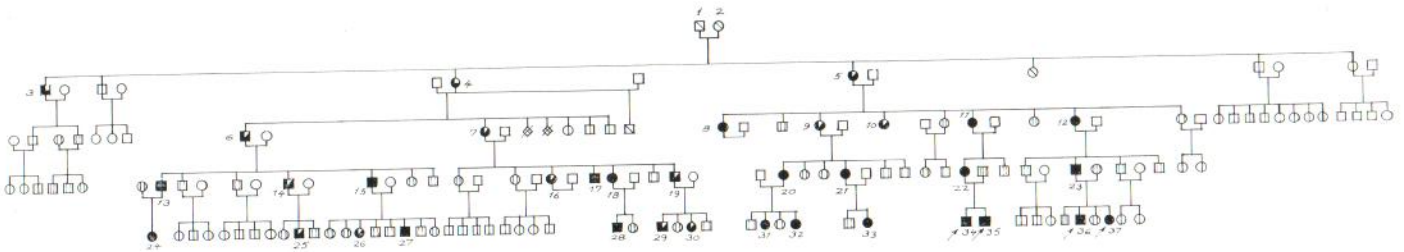


Fig. 1. Occurrence of epidermolysis bullosa dystrophica dominans in two families in the Faroe Islands. Fam. A: Genealogical table applying to family A. Fam. B: Genealogical table applying to family B.

- ■● Affected according to personal examination.
- ◪◕ Affected according to first degree relatives and/or mail contact.
- ◧◔ Affected according to second degree relatives.
- ◫◍ Unaffected according to personal examination.
- ◍◫ Unaffected according to first degree relatives or mail contact.
- ◫◯ Unaffected according to second degree relatives.
- □◯ Assumed unaffected from pedigree.
- ⊘ Unclassified.
- ⌀ Death in infancy.
- ◇ Sex unknown.
- ◒ Affected with malformation of nails as exclusive symptom.

Table II. *Total number of affected subjects; distribution of certain characteristics in living subjects in accordance with information obtained from these*

	Family A	Family B
Total number of affected subjects	37	36
Total number of living affected subjects	28	28
Malformation of nails	25	26
Malformation of nails, exclusive symptom	7	0
Congenital, local absence of skin	6	0
Congenital, local absence of skin, exclusive symptom	1	0
Tendency to bulla formation	20	28
Scar formation	20	28
Milia	12	8
Bulla formation involving mucous membranes	6	5
Excoriation due to removal of adhesive tape	3	3
Dental anomalies	1	7

was the only anomaly observed in 7 of the latter and one, a 4-year-old child, did not yet present symptoms other than congenital, local absence of skin on one foot.

All affected individuals in whom the tendency to bulla formation was manifest declared that the affection had made its first appearance at the time of their birth or shortly after.

All members of family A, apart from the small children, declared that the tendency to bulla formation had abated with age and almost all adult members maintained that it had subsided completely at the time of pubescence. On the other hand, among the 28 affected members of family B, 18 held that the disease admittedly had abated with age, but the tendency to bulla formation had not subsided after pubescence in any of these cases.

The severity of the disease might be of varying degrees in both families. In some cases there would merely be a development of bullae above the medial malleolus and on the knee, but in others, the almost permanent presence of bullae involving the ankles and the knees might be associated with lesions localized to the dorsal aspects of fingers, to elbows, the back, the shins, and the instep. The localization of bullae most frequently encountered was the medial region of the malleolus. Among other localizations, in general recorded according to rate of occurrence, were: the knee, the dorsal aspects of fingers, the elbows, the shins, the dorsal aspects of toes, the lateral malleolus, the area above the Achilles tendon, the palm of the hand (Fig. 3), the ulnar aspect of the wrist, the heel, the mucous membrane of the mouth, the medial edge of the feet, the back at the site of the spinous process, the chin, the bridge of the nose, the cheeks, sites above the acromion, theca cranii, and the external auditory meatus.

Mechanical traumata are generally responsible for the formation of bullae, mainly in the form of injuries to the ankle or the knee. In infants who kick their bare feet, the jarring of their heels will often be responsible, or they may clutch their toys with their hands; if they lie naked on a hard bed, kicking their feet, the skin above the spinous process may be injured.

Bullae of sizes varying from 2 mm up to 10 cm in diameter (Figs. 4 and 5) develop within intervals from 10 to 20 minutes after the trauma; eruption of the blisters will usually occur within a couple of days (Figs. 6 and 7).

It was admitted by all members of both families that the bullae left scars. Yet inspection of the previously affected areas of skin often failed to disclose these. In other cases, the patients' information of scar formation could be verified by thorough inspection especially of the area round about the medial malleolus at which site the skin would be thin, glistening, hairless and atrophic (Fig. 2).

Among the 56 affected subjects who were still alive, 5 had ostensibly no deformed nails. One of these was a 1-year-old child. The other 4 are living abroad and thus information about their nails was obtained via correspondence, not by personal examination. In some of the cases, the malformation of nails had set in shortly after birth, in others at much later stages. If in evidence, malformation of nails in all cases involved two or several toes, generally the big toe, malformation of fingernails was a less constant phenomenon and no more than 14 members of family A and 3 of family B had one or several deformed fingernails. The deformities might be of varying severity, ranging from total anonychia (Figs. 8, 9, and 10) to minor changes (Figs. 11 and 12).

It appeared that local absence of skin on one foot, or on both feet, had been a congenital phenomenon in 6 members of family A (Fig. 13).

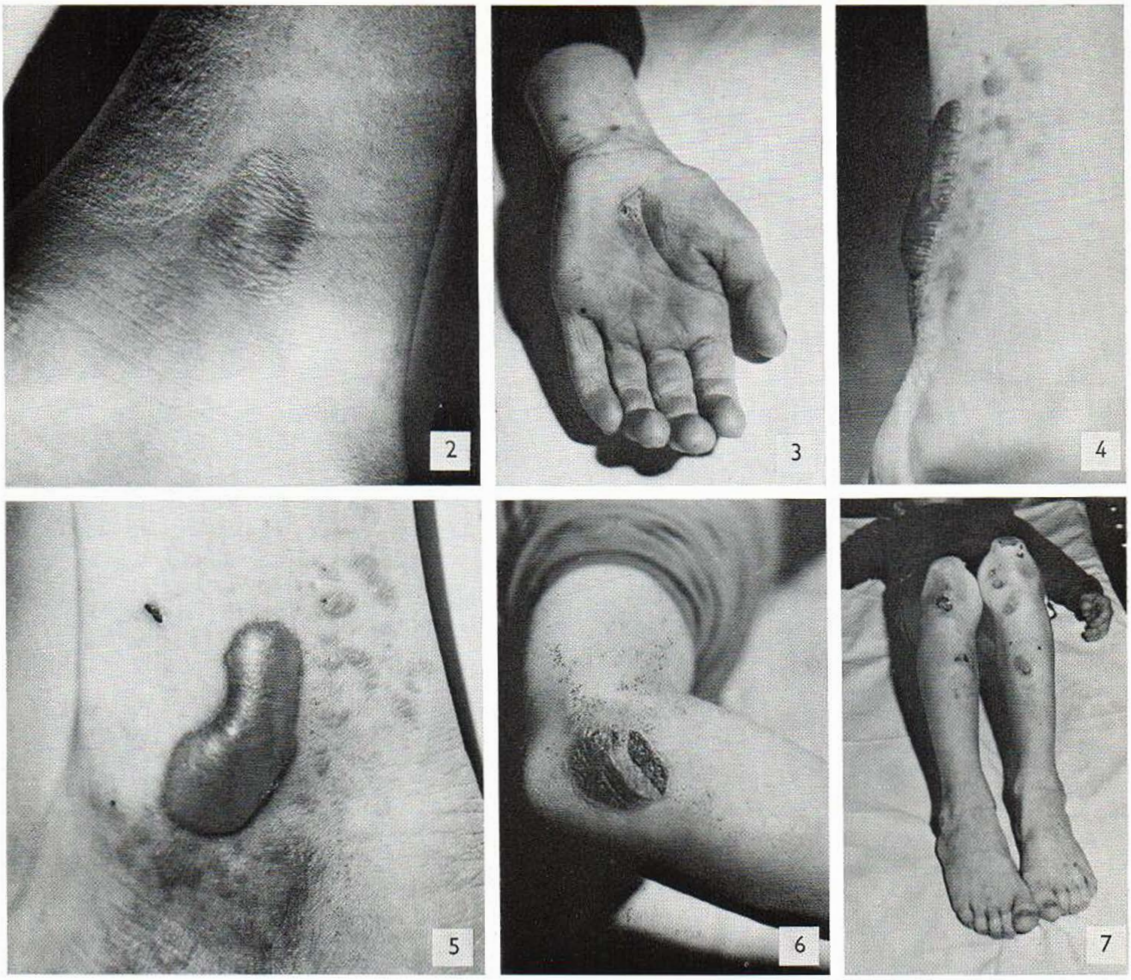


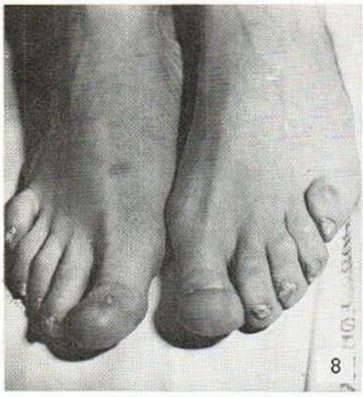
Fig. 2. No. 33, fam. A. Superficial scars left by bullae.
Fig. 3. No. 34, fam. B. Erupted bulla in the palm of the hand.
Fig. 4. No. 22, fam. B. Bulla 20 hours after onset.
Fig. 5. No. 22, fam. B. Bulla 20 hours after onset.
Fig. 6. No. 35, fam. B. Erupted bullae and wound formation; 8-year-old boy.
Fig. 7. No. 35, fam. B. Erupted bullae and wound formation; 8-year-old boy.

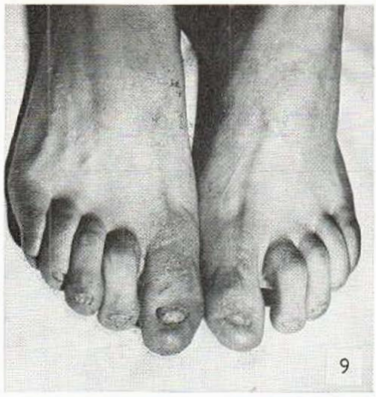
In fact, the questionnaires had not required information about such congenital absence of skin and those questioned provided the information on their own initiative; consequently, it cannot be excluded that this anomaly may have been manifest also in other cases.

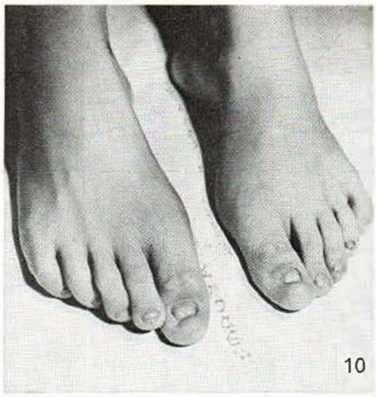
Formation of bullae involving mucous membranes was a rare occurrence and was never observed at sites other than the mucous membrane of the mouth. The chewing of dried fish or carrots, for instance, might be the causative trauma.

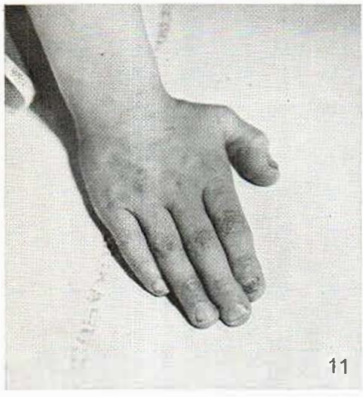
Dental anomalies were seen only in one member of family A in whom impaction of the four canine teeth was manifest. Dental anomalies were seen in 7 members of family B; these anomalies were in all cases moderate, mainly in the form of discolouration and/or skew tooth position.

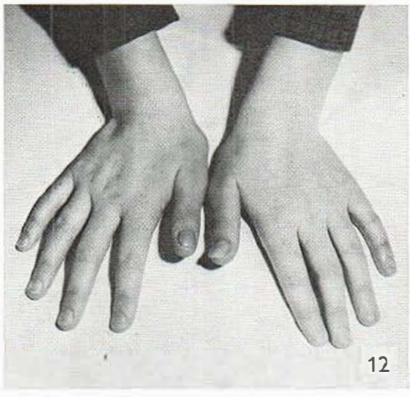
Most of the patients feel inconvenienced by the disease. Evaluation of the inconveniences vary from patient to patient; some attached major importance to the pain and smarting of the naked surfaces while others, mainly the young girls, suffered agonies because of their deformed nails; for instance, they could not go barefoot because people would stare at them. To the children it











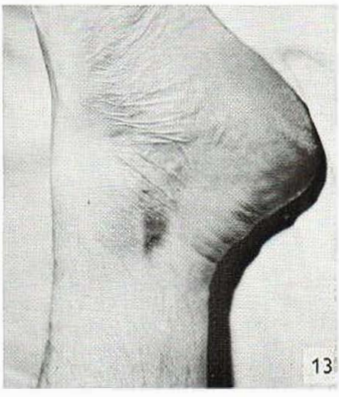


Fig. 8. No. 22, fam. B. Malformation of toe nails; 37-year-old woman.
Fig. 9. No. 23, fam. A. Malformation of toe nails; 40-year-old man.
Fig. 10. No. 33, fam. A. Malformation of toe nails; 10-year-old boy.
Fig. 11. No. 35, fam. B. Moderate malformation of finger nails; 8-year-old boy.
Fig. 12. No. 32, fam. A. Moderate malformation of thumb nails; 11-year-old girl.
Fig. 13. No. 23, fam. A. Glistening, atrophic skin, the sequela of congenital, local absence of skin of the left foot; 40-year-old man.

meant a nuisance always to be extra cautious during play if hurts were to be avoided and nails were not to be caught in doors, thereby provoking a development of bullae and malformations of nails.

GENETIC ANALYSIS

The affection has been manifest in members of family A throughout at least five successive generations, in members of family B throughout at least four generations. Non-affected carriers have not been detected in any of the families since non-affected children of affected parents marrying non-affected individuals in all cases bear non-affected children. It applies to all of those affected that one of the parents was affected, including nos. 3, 4, and 5 in family B, on the assumption that either no. 1 or no. 2 in family B had the disease and may even have been the mutant. Segregation and sex-ratios are in conformity with simple transmission by a dominant gene (Table III).

It applies to both families that the hereditary transmission of the disease is compatible with systematical transmission by a dominant autosomal gene although the degree of manifestation in family A admittedly varied to a certain degree in that the tendency to bulla formation was absent in 8 out of the 28 surviving members who carried the affection; in these cases, malformation of nails and/or congenital, local absence of skin were the only anomalies.

DISCUSSION

A thorough review of the literature seems to show that certain members of the two families discussed

Table III. *Ratios of segregation in families A and B*

Family	Affected parents	Sons		Daughters		In total	
		Affected	Non-aff.	Affected	Non-aff.	Affected	Non-aff.
A	9 ♂	7	13	8	14	36	50
	9 + 1[a] ♀	7	11	12 + 2[a]	12		
B	7 ♂	6 + 1[a]	11	3 + 1[a]	7	32	40
	10 ♀	5 + 2[a]	12	14	10		

[a] Probands.

in the present paper have been mentioned in other publications. For instance, it is apparently members of family A who are mentioned by Bülow & Nørholm-Pedersen in 1953 (2) and it is apparently some of the members of family B who are mentioned by Svend Lomholt in 1927 (7) and by Gunnar Lomholt in 1963 (6).

In their account of the incidence of epidermolysis bullosa hereditaria in Denmark, Bülow & Nørholm-Pedersen (4) mention two patients with epidermolysis bullosa dystrophica whose relatives live on the Faroe Islands. A small genealogical table applying to this family is recorded (Family VI). The reliability with which the pattern of this family can be traced in the reproduced tables is rather sound, the similarities suggesting that the subject recorded by B. & N.-P. may be descendants of subject no. 4 (Fig. 1 A). If so, the cases mentioned by Bülow & Nørholm-Pedersen should be identical with nos. 27 and 28 depicted in Fig. 1 A, this may very well be the case since the mother, subject no. 16, took up residence in Copenhagen when she was young.

On the assumption that it is a matter of identical subjects, a transmission by recessive genes, as suggested by Bülow & Nørholm-Pedersen, is not in evidence. On the other hand, it must be a matter of a systematic transmission by a dominant autosomal gene, phenotypically manifesting itself either in malformation of nails and a tendency to bulla formation or in malformation of nails exclusively. On the assumption that the two boys mentioned by Bülow & Nørholm-Pedersen actually are the sons of subject no. 15 (Fig. 1 A) it cannot be a question of a "partial shifting of type"; these two boys had, according to Bülow & Nørholm-Pedersen, died of congenital malformations immediately after birth, but it appears from the midwife's records and the mother's statement (subject no. 15, Fig. 1 A) that they had died at the age of 3 months, the cause of death being pneumonia, and that congenital malformations had not been in evidence in either of these boys.

The pathological pictures observed in the two families have certain features in common, for instance, the mode of development of blisters, their content, size, location, and healing. Milia and involvement of mucous membranes are seen in some patients in both families. Superficial scars left by bullae are manifest in almost all cases and it applies also to both families that the disease is systematically transmitted by a dominant autosomal gene. These findings suggest that both families are affected by epidermolysis bullosa hereditaria dystrophica, dominant form.

Even so, there is also a certain difference between the pathological pictures observed in the two families A and B. Above all, bullae never developed after the age of puberty in patients belonging in family A while such formation might continue to occur in all patients belonging to family B even after they had achieved adult age, though at a rate decreasing with age. Family A comprised 7 members in whom malformation of nails represented the exclusive symptom of the disease while a tendency to bulla formation was in evidence in all members of family B. It should be mentioned also that congenital, local absence of skin was in evidence in several patients belonging to family A whereas this symptom never occurred in members of family B.

As already mentioned, a thorough study disclosed that the ancestors of the two families were kindred, although kinship was rather remote. Hence, the involved pathological genes can hardly be assumed to be identical owing to the fact that

epidermolysis bullosa among descendants of the common ancestor was apparantly demonstrable only in individuals belonging to the two families discussed in the present paper. Taking into consideration also the essential difference in modes of manifestation, it might not be unreasonable to suggest that it is a matter of two dissociated families in which the hereditary type of epidermolysis observed in both may have many traits in common, yet remaining distinctly different.

Several of the features observed in family A are seen also in cases of the subtype EBDD (Bart) and, in conformity with findings reported by Bart (1), symptoms in these cases include: congenital, local absence of skin involving the lower extremities, periodic formation of bullae on skin and/or mucous membranes, malformation of nails, and systematical transmission by a dominant gene. According to Bart, these bullae were seen to heal without leaving scars while patients in family A declared that the bullae always left scars. As already mentioned, inspection of the previously affected areas of the skin frequently failed to disclose such scars. In other cases, the patients' information about scar formation could be verified by thorough inspection, especially of the area around the medial malleolus.

It has also been mentioned that a search for albopapuloid Pasini-papules was not made. Nevertheless, since it did not emerge from the numerous interviews with patients that such elements had been in evidence, it must be justified for the time being to classify the lesions observed in family B into subgroup EBDD (Cockayne-Touraine) on the consideration that they fulfilled the criterium: a congenital dominant EB involving malformation of nails and scar formation.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Mr John Davidsen for genealogical assistance, to Dr Hans D. Joensen, who called my attention to the affected children and, last but not least, to the numerous members of the two families for the readiness with which they supplied the information.

REFERENCES

1. Bart, B. J., Gorlin, R. J., Anderson, V. E. & Lynch, T. W.: Congenital localized absence of skin and associated abnormalities resembling epidermolysis bullosa. A new syndrome. Arch Derm (Chicago) *93:* 296, 1966.
2. Bülow, K. & Nørholm-Pedersen, A.: Epidermolysis bullosa heriditaria, arvelighedsforhold, prognose og forekomst i Danmark. Ugeskr Læg *115:* 479, 1953.
3. Gedde-Dahl, T., Jr: Epidermolysis Bullosa. A clinical, genetic and epidemiologic study. Universitetsforlaget, Oslo, Bergen and Tromsø, 1970.
4. — Phenotype-Genotype Correlations in Epidermolysis Bullosa. Birth Defects: Original Article Series. Vol. VII, No. 8; p. 107, 1971.
5. Köbner, H.: Hereditäre Anlage zur Blasenbildung (Epidermolysis bullosa hereditaria). Dtsch Med Wschr *12:* 21, 1886.
6. Lomholt, G.: Psoriasis, p. 209. Føroya Fróðskaparfelag, Tórshavn, 1963.
7. Lomholt, S.: Epidermolysis bullosa, med typisk familiær optræden. Dansk Dermatologisk Selskabs Forhandl, p. 29, 1927.
8. Pasini, A.: Dystrophie cutanée bulleuse atrophiante et albo-papuloide. Essai Clinique. Ann Derm Syph *9:* 1044, 1928.
9. Schnyder, U. V. & Eichhoff, D.: Zur Klinik der Genetik der dominant-dystrofischen Epidermolysis bullosa heriditaria. Arch Klin Exp Derm *218:* 62, 1964.

Received September 14, 1971

H. Debes Joensen, M.D.
84, Snebærhaven
2620 Albertslund
Denmark