

Inheritance in Epidermolysis Bullosa Letalis

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In 1935 Herlitz reported 8 cases of a 'new' type of recessively inherited epidermolysis bullosa. Because of the severe involvement and death in infancy he used the term 'epidermolysis bullosa hereditaria letalis' to describe these cases and 8 additional cases which had been previously reported (Mautner, 1922; Jenny, 1927; Heinrichsbauer, 1928; Kuse, 1929). The clinical characteristics as described by Herlitz (1935) are as follows: the bullae appear at or shortly after birth; they are frequently haemorrhagic and affect both skin and mucous membranes; the nails may be absent or later show marked dystrophy; and death usually occurs before the third month. Tendons and blood vessels may be seen through the transparent skin in affected areas. The identifying clinical feature is said to be the absence of scarring, pigmentation, or milia in areas of healing lesions. Since early death of recessive dystrophic cases could be responsible for the lack of these skin changes, some authors (Touraine, 1942; Muggler, 1963; Klunker, 1963) doubt the existence of a separate lethal category of epidermolysis bullosa. Those who do accept the lethal type as a distinct entity consider the inheritance to be autosomal recessive though detailed family studies have not been done.

A Kindred with Affected Members

This report describes a large kindred in which 14 members were affected with a severe, lethal form of epidermolysis bullosa.

Clinical Features. Clinical data on all patients were obtained from interviews with the parents. Only 3 patients were admitted to hospital and one of these (X. 31 (see Fig. 1)) was examined by one of us (H.E.C.) during life; interview data on one other hospitalized patient (X. 19) were supplemented by medical records and necropsy reports.

None of the mothers reported an abnormal pregnancy

with any patient and no drugs were taken during gestation. None of the children was premature by weight and two weighed more than 4.1 kg. (9 lb.) at birth. The dizygotic twins (X. 18 and X. 19) were approximately 2.7 kg. (6 lb.) and 3.2 (7 lb.), respectively. In one family (IX. 1-9) two additional sibs died with spina bifida, but all other sibs were normal.

Although the mouth was always affected with bullae and consequent eroded areas, no difficulty was experienced with feeding or swallowing. Most patients had no vomiting or diarrhoea, though one (X. 31) required a liquid diet in order to maintain nutrition. An initial weight gain was never continued, however, and all lost weight before they died.

Blisters frequently became secondarily infected. Four children had pyrexia and convulsions immediately before death, but no other illnesses were diagnosed during life. In particular, no respiratory infections were reported. None of the patients was given systemic cortisone, and local treatment seemed to be most effective when it dried the lesions.

Of the 14 affected children, 9 were male and 5 were female. Eleven of the infants died by 8 weeks of age, the youngest at the age of 2 weeks. Two lived for 9 months and one for 14 months. The latter was continuously in hospital from the age of 6 weeks.

Skin lesions. Bullae were occasionally noted at birth and within 24 hours some erythema and blistering developed at the base of several finger-nails. This was usually followed by shedding of the affected nails and infection of the nail-beds. Regrowth of nails was rarely observed. During the neonatal period the bullae were often haemorrhagic and developed on all areas of the body except the palms and soles. Some of the areas affected by blisters remained erythematous and in rare cases became covered by transparent, atrophic tissue. Dystrophic scars, pigmented areas, and milia were never seen. The epidermis was fragile, and it was often impossible to handle the infants without traumatizing the skin. The mouth was always involved with bullae, and lesions were also generally present in the anterior nares. No ophthalmological abnormalities were noted.

Pathological Features. Necropsy was performed on only one patient (X. 19). He was grossly under-

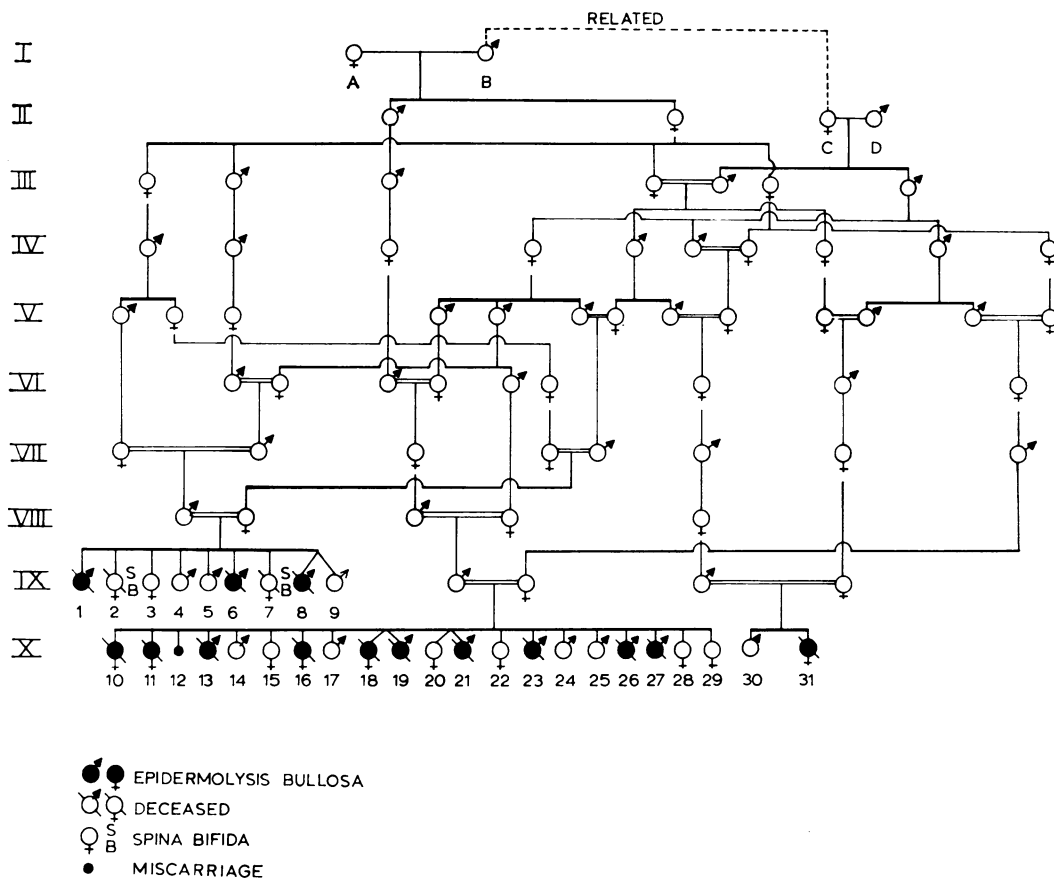


FIG. 1. Pedigree of Amish epidermolysis bullosa cases. All parents can be traced to either couple I.A-I.B or II.C-II.D. Since I.B and II.C were related, some ancestor common to both probably introduced the gene to the Amish.

developed and severely emaciated; and the most striking changes were the widespread skin lesions evident around the mouth, nose, and eyes where there were confluent erosions with haemorrhagic encrusted borders (Fig. 2a). Large eroded areas were seen on the right elbow, back (Fig. 2b), and lower legs. Haemorrhagic bullae were present at the base of the nails and many finger- and toe-nails were missing. Blisters and eroded areas were widely distributed on the trunk and limbs. No milia, pigmented areas, or dystrophic scars were seen, nor was it possible to see blood vessels or tendons in the more severely affected areas (e.g. on the right elbow, Fig. 2a). Ulceration was also noted on the posterior surface of the tongue and most of the pharynx.

Histological material showed all stages of the disease. Sections of skin from the toe demonstrated areas of dermal-epidermal separation (Fig. 3a). The plane and cleavage followed the irregular contour of the rete ridges and descended part of the distance along the dermal-epidermal junctions of hair follicles and sweat ducts. Parakeratosis was not present and vacuoles in the epidermal basal cells were infrequent and unrelated

to the margins of the bullae. Blister fluid, dermal oedema, and inflammatory cells were inconspicuous in the minimal (earliest) lesions. Other sections with more extensive bullae showed degenerative changes in the overlying epidermis. Both blister and dermal oedema were seen (Fig. 3b). The inflammatory changes at this stage ranged from small aggregates of plasma cells to a denser mixed infiltrate, including occasional cells in the blister fluid. The edges of the bullae were sharp rather than blunted and an acute angle was formed between the dermal and epidermal layers. No evidence of secondary regeneration was seen in the material from this case. A section of abdominal skin showed the most advanced changes (Fig. 3c). The epidermis was absent, and encrusted necrotic debris formed a partial dermal covering. The superficial dermis had the appearance of non-specific granulation tissue characterized by proliferating capillaries, chronic inflammatory cells, and relatively dense collagen. The lower dermis was unremarkable and the only abnormality in the adnexa was dilatation of eccrine ducts.

The section through the posterior tongue (Fig. 4)

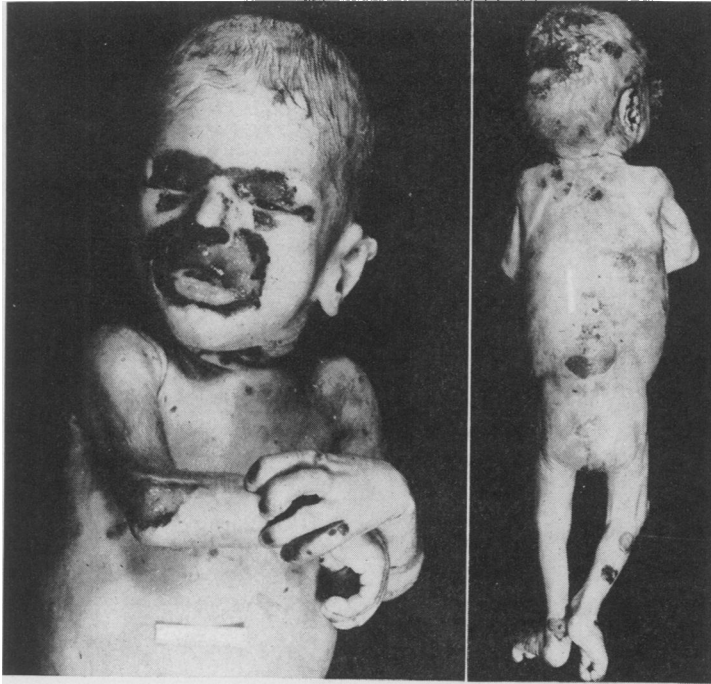


FIG. 2. Post-mortem photograph of X.19. (a) Large confluent lesions with haemorrhagic encrusted borders are present around the mouth, nares, and eyes. An extensive lesion involving all layers of the skin is present on the right elbow. The finger-nails are absent, the left ear is deformed, and there is moderate hirsutism on the arms. (b) Note severe emaciation and multiple lesions of all sizes over the trunk and extremities.

showed an ulcer and foci of epithelial separation that were identical to the changes in the skin. Plasma cells were present around the ulceration and under the adjacent papillae. No diagnostic changes were found in the remaining tissues.

The epithelium was partially detached in the sections of trachea and gall-bladder, but post-mortem artefacts could not be excluded as the cause and no abnormalities were seen in the underlying tissues.

Genetic Aspects. These patients belong to the Old Order Amish, a highly religious and ultraconservative Protestant sect with origins in Switzerland nearly 300 years ago. All Amish today live in genetic isolates in the United States and Ontario. Each isolate is a closed, self-defined population to which almost no new genes have been added since immigration ceased in the 1850's. Because of the small number of original settlers, the small size of the isolates, and the subsequent strict endogamy, a relatively high mean coefficient of consanguinity exists.

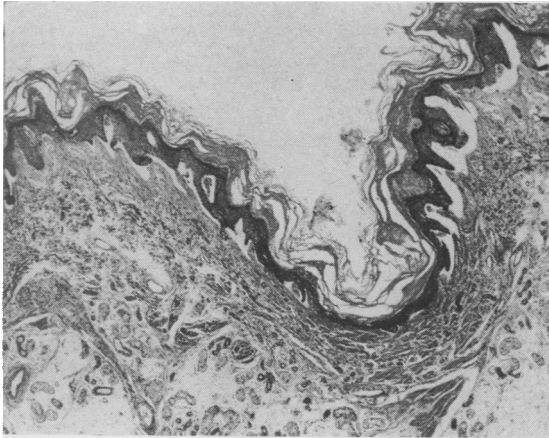
In an endogamous population with few founders, such as the Amish, the common ancestor approach can be used to suggest autosomal recessive inheritance in certain disorders. Fig. 1 shows that all six parents in the present study share a single ancestral couple, I. A. and I. B. Alternate pathways are available for the gene since another couple (II. C and II. D) is also common to

all parents. Moreover, indirect evidence (recorded in a study on the Mast syndrome) suggests that I. B and II. C were sibs or at least closely related (Cross and McKusick, 1967). It is likely that an unidentified heterozygous ancestor contributed the epidermolysis bullosa gene to both I. B and II. C.

The Amish originated in the Canton of Berne in Switzerland about 1693 but no Amish live there today. At least 2 reports have described recessively inherited epidermolysis bullosa in 20th century Swiss families. Jenny (1927) reported 5 families with the presumed lethal variety who lived in the Canton of Aargau. Later, Schnyder, Jung, and Šalamon (1964) found 9 cases of recessively inherited epidermolysis bullosa in Switzerland and, though no distinction was made between the dystrophic and lethal types, it is possible that at least some of these patients did have the lethal type.

Discussion

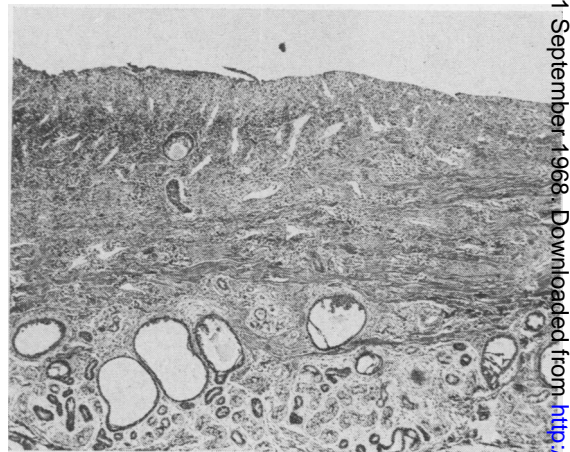
Clinical Considerations. The recognized types of epidermolysis bullosa (Table I) can usually be distinguished clinically and genetically. There are, however, two exceptions. First, it is not possible to differentiate between dystrophic autosomal recessive cases and some sporadic cases of the dystrophic autosomal dominant type. Secondly, severely affected patients with the recessive



(a)



(b)



(c)

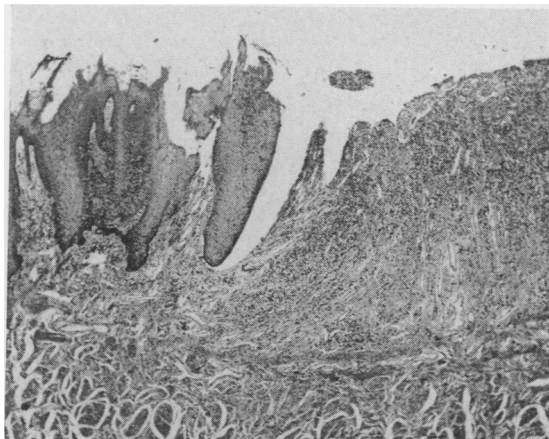


FIG. 4. An area of epithelial separation and erosion on the posterior tongue. A plasma cell infiltrate is seen in the area of necrosis (right) and underlying the adjacent papillae (H. + E. $\times 25$.)

FIG. 3. Sections of skin. (a) Section from toe showing nearly complete epidermal-dermal separation in the absence of secondary changes. The line of cleavage follows the irregular contour of the rete ridges (H. + E. $\times 30$.) (b) A later lesion characterized by degeneration of the overlying epithelium and oedema and moderate inflammatory infiltrate in the superficial dermis. Neither secondary epidermal regeneration nor scarring are present. (H. + E. $\times 30$.) (c) The chronic ulcerative lesion from abdominal skin has the appearance of non-specific granulation tissue. The only abnormality in the deeper dermis is dilatation of the eccrine ducts (H. + E. $\times 30$.)

TABLE I
CLINICAL AND GENETIC CHARACTERISTICS OF EPIDERMOLYSIS BULLOSA

Mode of Inheritance	Clinical Category	Clinical Features
Autosomal dominant	Epidermolysis bullosa simplex	Onset usually within the first two years; bullae precipitated by heat rather than trauma, and heal without scarring; bullae usually subcorneal or intra-epidermal when sectioned
	Epidermolysis bullosa simplex hands and feet	Onset often in first two decades; bullae on feet more than hands, and heal without scarring
	Epidermolysis bullosa dystrophica	Onset at birth or early infancy; bullae precipitated by trauma rather than heat, and heal with scarring; mainly on extremities; mucous membranes usually involved; dystrophic changes in nails; epidermal cysts; bullae are subepidermal when sectioned
Autosomal recessive	Epidermolysis bullosa dystrophica	Onset at birth; mucous membranes often involved, conjunctivae may be affected, atrophy of teeth, and strictures of oesophagus and pharynx may occur; pigmented areas may be seen; scarring, epidermal cyst formation, and nail dystrophy invariably present; may develop syndactyly and dwarfism; bullae are subepidermal and may be haemorrhagic
	Epidermolysis bullosa hereditaria letalis	Onset at birth; severe involvement of skin and mucous membranes at birth, and nails commonly abnormal; usually die in first three months; bullae show little tendency to heal and are subepidermal

dystrophic type and cases of the recessive lethal condition described by Herlitz (1935) may be clinically indistinguishable.

The clinical features of the Amish cases are compatible with those previously published for epidermolysis bullosa hereditaria letalis. In particular, the lesions shown in the post-mortem photographs (Fig. 2) resemble those in the reports of Herlitz (1935), Henderson (1955), and Roberts and co-workers (1960). Characteristically, lesions were first noticed at the base of the nails, and later on the trunk, face, scalp, and extremities. Palms and soles were never involved and no dystrophic changes, pigmentation, or milia were seen. Some healing was noted but the skin still appeared abnormal in these areas. No scarring was present, even in the two patients who lived until 9 and 14 months of age.

Detailed morphological alterations have been described by Roberts and co-workers (1960). It was their opinion that the cleavage resulted from coalescence of intracellular vesicles in the germinal epithelium. They also called attention to the morphological similarity between the bullae in their cases and those which follow basal cell degeneration (lichen planus, incontinentia pigmenti, and lupus erythematosus). The ultrastructural findings in another case (Pearson, 1962) suggest that the defect is in the intermembranous space separating the basal and dermal cells.

Extra-epidermal lesions have been described in previous reports (Roberts *et al.*, 1960; Maddison and Barter, 1961; Leland and Hirschl, 1954) of epidermolysis bullosa letalis. These have con-

sisted of vesicular changes in the trachea and bronchioles similar to those seen in the skin (Maddison and Barter, 1961; Leland and Hirschl, 1954), suggesting that the lesions in the integument are only part of a more widespread abnormality. Lesions have also been reported in the pancreatic and biliary ducts (Roberts *et al.*, 1960; Maddison and Barter, 1961). The respiratory tract and the pancreatic and biliary ducts, however, are locations in which epithelial separation may result from poor tissue preservation. The present case demonstrates unequivocal evidence of epithelial lesions since the oral ulcerations were noted before necropsy and the tongue is relatively resistant to autolysis.

The classification of epidermolysis bullosa must at present be based on clinical and genetic characteristics alone, since biochemical and pathological studies have not yielded definitive diagnostic criteria. Histological studies of specimens from patients with both recessive dystrophic and the lethal types suggested that bullae form at the dermo-epidermal junction. However, Pearson (1962) described ultrastructural changes in epidermolysis bullosa letalis, which suggested that separation occurred in the plane of the intermembrane space, i.e. between the cell membranes of the epidermal and dermal layers. By contrast, study of 5 patients with recessive dystrophic type showed the earliest changes in the basal cell layer. These findings suggest that the lethal type has a pathogenesis different from the other varieties, but this has been challenged by electronmicroscopy studies in another patient (Lapière, Castermans-Elias, and Firket, 1964).

TABLE II
REPORTED FAMILIES OF EPIDERMOLYSIS BULLOSA LETALIS

Reference	No. Affected		Number Unaffected	Age at Onset (days)	Age at Death (days)	Parental Consanguinity
	Male	Female				
Jenny (1927)		1	1	1	40	Second cousins Fifth cousins, once removed Fourth cousins
		2	2	1	35; 155	
		1	12	1	10	
		2		1	10; 180	
Heinrichsbauer (1928)	1			1	240	
Kuse (1929)	1	1	1	1	3	
Herlitz (1935)	2	2	1	1	300	
	1	1		1	17-100	
	2			1	35	
Davidson (1940)	1			1	14; 25	
Brandberg (1941)		1		3	99	
Black <i>et al.</i> (1945)	2	1	2	1	5	
Schäffer (1951)	1	1	1	1	29-74	First cousins
Leland and Hirschl (1954)	1	1	1	1, 2	27; 40	
Frank and Kern (1954)		1	1	1	19; 66	
Calnan (1954)		2	1	1	?	
Henderson (1955)		1	1	1	60; 200	
	1	2	4	11	180	Third cousins
Lucini (1955)		1		1	21-120	
Mercuand Compay Tiziano Zago (1955)		2	4	1		
Lewis, Steven, and Farquhar (1955)	1			1	35, 41	
	2		2	1	70	First cousins
	1	2		5	70	
Rosset (1956)	1	1		1	1-6*	
Silver (1957)	1	1	2	1	†	
Roberts <i>et al.</i> (1960)		1		1	24	
	1			1	20	
Maddison and Barter (1961)		1	1	1	42	
		1	1	1	9	
Cox (1961)		1	1	1	35	
Bergenholtz <i>et al.</i> (1963)	1		1	1	21	
Klunker (1963)		2	1	1	19 mth.	
Lapière <i>et al.</i> (1964)		2	1	1	55; 58	
Schwob (1965)	1		1	1	120	
Present cases	3		6	1	4	
	6	4	9	1	14-28	See pedigree
		1	1	1	30-430	See pedigree
			1	1	226	See pedigree
Subtotals	32	40	55			
Mautner (1922)		3		1	14-66	
Schroder and Wells (1945)	1			Birth	5	
Lamb and Halpert (1947)		1		Birth	50	
Matheson and Rosner (1949)		1		Birth	2	
Pearson (1962)	1 (?)			?	?	
Totals	34	45				

* One patient was still alive at 30 months of age.

† Patients were alive at 30 months and 2 months of age.

Genetic Considerations. Although inheritance of the lethal type of epidermolysis bullosa is presumed to be autosomal recessive, no genetic analysis has been done on the total number of cases reported. Because of the strong evidence of autosomal recessive inheritance in the Amish cases, it is of interest to determine if the consanguinity rate and the segregation ratio of previously reported families are consistent with this mode of inheritance.

Epidermolysis bullosa letalis is a rare disorder; including the present report there are only 79 cases on record (Table II). Criteria for inclusion of cases with the Herlitz lethal form of epidermolysis bullosa were as follows: onset of disease in the neonatal period; death or absence of remissions in the first three months of life; and absence of milia,

pigmentary changes, and scarring. Since many reports do not comment on parental consanguinity and others contain inadequate family data, only selected families can be used for genetic analysis. Among 38 families (upper portion, Table II) in which family data were reported, the parents were definitely known to be related in 9 families. Even if it is assumed that there was no consanguinity in the families about which no statement was made, the consanguinity rate would be 9/38, or 24%. It is difficult to obtain an 'average' consanguinity rate for the world population from which these cases were reported but it is certainly much less than 24%, and probably no higher than 4 or 5%.

Segregation analysis in reported families is usually complicated by lack of information con-

cerning the methods of ascertainment and selectivity of reported cases (Morton, 1959; Steinberg, 1959). For practical purposes the families in Table II may be considered as having been ascertained by single ascertainment, i.e. the probability that a family has been reported is dependent on the number of affected offspring, but only one individual served as the proband in each family. If a significant number of the families in Table II were ascertained because of relatedness of previously ascertained probands (multiple ascertainment), then these assumptions clearly would not be valid. However, with the exception of one of the Amish sibships reported here, and possibly two of Jenny's (1927) families, none of the sibships in Table II are known to have been ascertained in this manner. The proband method of segregation analysis may thus be used since it becomes fully efficient and identical to maximum likelihood methods as ascertainment approaches single ascertainment (Steinberg, 1959). The proportion of affected sibs by this method is 34/111, or 0.306, for the 38 families in the upper portion of Table II for which adequate family data were available. The standard deviation of this estimate is 0.044 and the 95% confidence limits are 0.218 to 0.394.

At the present time, evidence for the existence of a separate lethal form of epidermolysis bullosa is only suggestive. It must be remembered, however, that when a category of genetic disease is studied closely with combined clinical, genetic, and biochemical approaches, heterogeneity is usually found within what previously appeared to be one entity. Illustrative examples among skin diseases are albinism, ichthyosis, tylosis, the ectodermal dysplasias, and alopecia congenita. The classification of epidermolysis bullosa has followed a similar pattern in the past, and new evidence will no doubt produce new categories.

No doubt some recessive dystrophic patients die before they develop scarring or pigmentary changes, and certainly some patients with the lethal type live longer than the three-month period characteristic of Herlitz' cases. In such instances differentiation on clinical grounds alone may not be possible. It is significant, however, that no sibship has yet been reported in which affected individuals with dystrophic scarring were closely related to affected individuals who survived longer than a year and who lacked scarring and pigmentary changes. Jenny (1927) reported five families belonging to a single kindred who had a lethal form of the disease. Muggler (1963) attempted to connect all of Jenny's families with a large pedigree of several families with the presumed recessive dystrophic variety since

all came from the same canton of Switzerland. The critical genealogical evidence was not available, however, since the common ancestors of Jenny's cases were different from those of the dystrophic cases.

If a lethal variety of epidermolysis bullosa is accepted by present criteria, the pedigree of the Amish cases, the increased parental consanguinity in reported families, and segregation analysis all suggest autosomal recessive inheritance.

Summary

Three Old Order Amish families with 14 cases of epidermolysis bullosa are presented. The clinical features of these cases are similar to those found in the Herlitz or lethal form of epidermolysis bullosa. Pathological material in one patient revealed lesions in all stages of the disease and an unequivocal extra-epithelial lesion on the tongue. All parents can be traced to two related immigrant couples.

A review of the literature revealed 65 additional cases with the Herlitz type of epidermolysis bullosa. In these cases as well as in the Amish families reported here, increased parental consanguinity and segregation analysis are consistent with autosomal recessive inheritance.

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