Epidermolysis Bullosa

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The term epidermolysis bullosa is applied to a group of conditions where vesicles occur most commonly on the skin but sometimes on mucous membranes. The content of these vesicles is serous but may become turbid or haemorrhagic, and secondary infection sometimes occurs. Apart from a type that may follow administration of sulphonamides (Bloom, 1953), all forms appear to be genetically determined at single gene loci. Further, all cases appear to be determined by autosomal mutations, with the exception of the patients in one family where epidermolysis bullosa appears as part of a widespread syndrome determined by a sex-linked gene. This family first described by Mendes da Costa and Van der Valk (1908) has subsequently been reported by various authors over a number of years under varying titles: perhaps the most generally used at the present time being dystrophia bullosa, typus maculatus (Woerdeman, 1958).

Determination by autosomal dominant and recessive genes has long been known and, as is usual in other traits where this phenomenon is found, the recessive forms are on the whole more severe in their effects. However, in epidermolysis bullosa there appears to be considerable overlapping in severity of forms determined in the two ways. The most distinctive clinical finding is whether or not scarring follows the healing of lesions (Pearson, 1962; Schnyder, Jung, and Salamon, 1964). This division corresponds to 'dystrophic' and 'simplex' (non-dystrophic) forms. It has been demonstrated by Johnson and Test (1946) that in the simplex type the blisters form in the epidermis or are subcorneal, while Touraine (1942) showed that in the dystrophic form the blister formation was subepidermal.

Parent Investigation

Ascertainment of Cases in the Oxford Area. In 1962 all general practitioners in the Oxford

Regional Hospital Board area were asked to notify cases of epidermolysis bullosa. First notification of 12 cases was from this source. In addition the six consultant dermatologists in the area notified all cases seen by them and subsequently they reported new cases as seen. Twenty-two index patients first became known through dermatologists.

Four individuals could not be traced and in two notified patients the diagnosis was not confirmed, so that in all 28 families were ascertained through index cases. It was realized that ascertainment was incomplete and it was decided not to make more determined efforts as it was soon obvious that all severely affected cases were known to dermatologists while many subjects with milder types simply regarded themselves as prone to blistering and never attended a doctor. In the following discussions of clinical aspects, an additional family seen in Northern Ireland is considered, so that in all 29 families were seen.

In all these families at least one member had been seen by a dermatologist. In 10, only one member was affected. In the 19 families with more than one affected the pedigree suggested dominant gene inheritance in 17 and recessive gene inheritance in two.

Clinico-genetic Grouping of Cases. The most clear-cut division of cases where more than one case occurred is on the basis of mode of inheritance. As already noted, the primary clinical separation is on the basis of severity-scarring or dystrophic and non-scarring or simplex. It seems likely that the recessive form is always dystrophic, never simplex, and that the dominant form is more commonly milder or simplex. The dominant simplex form appears to have two variants, one where only the feet are affected (Cockayne, 1938), and one where the blisters are widespread though most commonly occurring on the extremities. The family cases therefore fall into three (or four) groups—dominant simplex (dominant Cockayne), dominant dystrophic, and recessive dystrophic.

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TABLE I

CLINICAL FINDINGS IN 77 PATIENTS WITH EPIDERMOLYSIS BULLOSA CLASSIFIED ACCORDING TO MODE OF INHERITANCE

	Dominant					Dominant Dystrophic			Recessive Dystrophic		
	Simplex		Cockayne Type		Total	Dominant	Sporadic	Total	Recessive	Sporadic	Total
	Dominant	Sporadic	Dominant	Sporadic							
No. of cases	34	5	10	1	50	20	1	21	3	3	6
Onset under 1 yr.	13 (38)	1	7 (70)	—	21 (42)	20 (100)	1	21 (100)	3	3	6
Affected sites											
Hands	16 (47)	5	—	—	21 (42)	11 (55)	1	12 (57)	3	3	6
Elbows	2 (6)	—	—	—	2 (4)	9 (45)	1	10 (48)	3	3	6
Feet	31 (91)	3	10 (100)	1	45 (90)	6 (30)	1	7 (33)	3	3	6
Ankles	4 (12)	—	—	—	4 (8)	15 (75)	1	16 (76)	3	3	6
Knees	3 (9)	—	—	—	3 (6)	14 (70)	1	15 (71)	3	3	6
Trunk	3 (9)	1	—	—	4 (8)	1 (5)	—	1 (5)	—	3	3
Mucous membrane	—	—	—	—	—	1 (5)	1	2 (10)	—	3	3
Teeth	—	—	—	—	—	—	—	—	—	—	—
Scarring	1 (3)	—	—	—	1 (2)	18 (90)	1	19 (90)	3	3	6
Epidermal cysts	—	—	—	—	—	11 (50)	1	12 (57)	3	3	6
Finger- or toe-nail dystrophy	5 (15)	—	2 (20)	—	7 (14)	16 (80)	1	17 (81)	3	3	6
Precipitated by heat	33 (97)	2	8 (80)	1	44 (88)	1 (5)	—	1 (5)	—	—	—
Precipitated by trauma	17 (50)	—	—	—	17 (34)	20 (100)	1	21 (100)	3	3	6

Figures in parentheses are percentages.

Sporadic cases where there is no parental consanguinity may be distributed on clinical grounds alone under these headings, which will be considered seriatim. Relevant clinical features of the cases seen are set out in Table I.

Dominant Epidermolysis Bullosa Simplex. In the 9 families so classified, there were 48 living affected subjects, and of these, 34 were examined. Only a few showed bullae at the time of examination. The history was of early onset with the blisters affecting the hands and feet (the latter in 91%). As will be seen from Table I blisters occurred elsewhere on the body and in 5 patients there was some nail dystrophy. The one in whom minimal scarring occurred was probably due to hygienic neglect and secondary infection. These patients were most commonly affected in the summer and there appeared to be no susceptibility to blistering with age, but one woman of 28 had had no blisters since puberty. Segregation analysis in these families did not show any significant variation from an expected ratio of affected to

unaffected of 1 : 1 in the offspring of affected individuals, and males and females appeared to be affected equally (Table II).

Of the 10 sporadic cases, 5 appeared on clinical grounds to fit into this group (Table I).

Dominant Epidermolysis Bullosa (Cockayne). In four families 10 of the 24 living affected subjects were examined: the bullae occurred only on the feet. The age of onset in 7 of the 10 was under 1 year of age, and in 2 there was some dystrophy of the toe-nails. In this form also the major precipitating factor appeared to be heat. Again, there was no difference from an expected 1 : 1 ratio of affected to unaffected in the offspring of affected parents, and there was no significant disturbance of the sex ratio (Table II). There was one sporadic case which appeared to fit into this clinical category.

Dominant Epidermolysis Bullosa Dystrophica. In 4 families examinations were carried out on 20 of the 37 living affected subjects who had the dystrophic form of epidermolysis bullosa as judged by

TABLE II

DISTRIBUTION OF DOMINANT EPIDERMOLYSIS BULLOSA BY SIBSHIP SIZE IN OFFSPRING OF ALL KNOWN AFFECTED MEMBERS IN 17 FAMILIES

Sibship Size	No. of Sibships	Affected				Unaffected			
		Males	Females	Sex Unknown	Total	Males	Females	Sex Unknown	Total
1	7	2	5	—	7	—	—	—	7
	12	1	7	—	8	3	1	—	4
2	12	4	10	—	14	2	8	—	10
	5	3	3	—	6	2	2	—	4
	3	3	2	—	5	1	—	—	1
3	9	7	5	—	12	4	7	4	15
	1	1	—	—	1	—	2	—	2
	4	6	3	—	9	1	2	—	3
4	5	6	4	—	10	7	2	1	10
	1	—	2	—	2	2	—	—	2
	3	3	4	—	7	2	2	1	5
5	4	4	3	—	7	9	4	—	13
	1	2	—	—	2	2	1	—	3
	4	4	7	2	13	3	3	1	7
6	—	—	—	—	—	—	—	—	—
	1	1	—	—	—	—	—	—	—
	—	—	—	2	3	—	—	3	3
7	1	—	1	—	1	5	1	—	6
	1	4	2	—	6	—	1	—	1
8	—	—	—	—	—	—	—	—	—
	1	3	4	—	7	1	—	—	1
9	—	—	—	—	—	—	—	—	—
	1	4	1	—	5	2	2	—	4
	—	—	—	—	—	—	—	—	—
Total	39	27	29	—	56	29	24	5	58
	10	13	11	—	24	7	6	—	13
	27	18	23	4	45	10	8	5	23

Upper figure in each column = epidermolysis bullosa (simplex)

 $\chi^2 = 0.14$; d.f. = 1; $0.80 > p > 0.70$.

Middle figure in each column = epidermolysis bullosa (Cockayne)

 $\chi^2 = 3.27$; d.f. = 1; $0.10 > p > 0.05$.

Lower figure in each column = epidermolysis bullosa (dystrophica)

 $\chi^2 = 7.12$; d.f. = 1; $0.01 > p > 0.001$.

the presence of scars or epidermal cysts. In each of these 20 subjects bullae had occurred in the first year of life and in many they were noted shortly after birth. Trauma rather than heat was the predominant precipitating factor in these patients and this appears to be reflected in the distribution of lesions (Table I). In 16 subjects there was dystrophy of the nails, of the fingers or toes, and in one the mucous membranes were affected. Most patients commented that they had less trouble with the condition as they grew older, but this might have been due to the fact that they took more care to avoid trauma.

In the families showing this type of the disorder in the offspring of affected parents there were 45 affected and only 23 unaffected, which is

significantly different from the expected ratio 1 : 1 at a 5% probability level (Table II). The sex ratio in the affected (18 : 23) did not appear to be disturbed. In one of these families the mother of the index case was illegitimate and though details of other members were obtained they were not examined, so that the pedigree probably was not accurate. Two affected female subjects admitted that they had limited the size of their families once they had had an affected child, and one of these had been sterilized. Even if only the members of the last two generations were considered, affected parents had 24 affected and 15 unaffected offspring, but this ratio 1.6 : 1 was not significantly different from the expected 1 : 1 ratio. There was no evidence that the con-

tribution to the disturbance of the segregation ratio was determined by the sex of the affected parent.

There was only one sporadic case that appeared to fit into this category (Table I). This was a woman aged 28 years who was moderately severely affected. Since completing this study she has been delivered of her first child who was noted to have a bulla on the mucous membrane of her mouth and some bullae on the lower limbs. These findings are rather suggestive of epidermolysis bullosa, and it will be of interest to follow up this child.

Recessive Epidermolysis Bullosa Dystrophica. There were only two families with cases of dystrophic epidermolysis bullosa, where the pedigrees were compatible with recessive inheritance. There was no evidence of any consanguinity in the parents. In one family, 2 out of 3 sibs were affected and both were seen. The lesions were most widespread on the limbs and there had been no improvement with age. In the other family there were 3 affected members in the sibship of 9. Only one of them could be seen. It was reported that the affected brother and sister had respectively 2 and 7 unaffected children.

One of the three sporadic cases with the dystrophic form, which by reason of severity were placed in the recessive group, is of some interest. The child, a male, was born with blisters on the side of the face and on the oral mucosa and very severe blistering of the hands and feet. When first seen about ten days after birth by a colleague in this Unit, he was extremely ill with massive bullae covering the hands and feet, and shortly afterwards the right great toe sloughed away. He was treated with corticotrophin and he slowly improved. When seen at 4½ years the boy was found to have multiple scars, epidermal cysts, and nail dystrophy. If this child had died in hospital the cause of death would undoubtedly have been his skin condition.

Frequencies. Frequency estimates from the data reported must be regarded as minimal. In all 77 patients were examined, but though all but one index case of each family was in the Oxford area, only 41 of the affected lived in the area served by the Oxford Regional Hospital Board which has a population of about 1,700,000. In addition, there were known to be another 49 living affected subjects in these families who were not examined. This problem of scattering of families outside the area where the population of defined size lives often occurs with mild dominant genes where families are large. Where there are a large number

of families and the condition is relatively homogeneous clinically and genetically, some arbitrary decisions can be taken as to which families are to be excluded and which included in the frequency estimates, but this is not possible with the small number of cases in each group which is homogeneous both clinically and genetically. A minimal estimate of the frequency of all dominant types taken together is probably about 1:50,000. This is minimal because undoubtedly the mildest cases are not ascertained and indeed appear to shade into nonentity.

The 6 cases with the recessive form of epidermolysis bullosa ranged in age from 4 to 38 years and a minimal estimate of the frequency is about 1:300,000.

Linkage. In recent years linkage has been found between the genes of certain of the blood groups and rare abnormalities where the mode of inheritance is known, for example ABO and nail patella syndrome (Renwick and Lawler, 1955), and Rhesus and elliptocytosis (Lawler and Sandler, 1954). Seven families with dominant epidermolysis bullosa were selected for linkage studies and the following blood group systems were examined: ABO, Rhesus, MNS, P, Kell, Lewis, Lutheran, Duffy and Kidd. One affected child, family No. 29 V. was found to be illegitimate but no further details were obtained. The data for some of the families were incomplete. Using the sib pair method of Penrose (1953), there was no evidence of linkage between the loci for ABO, Rhesus, MNS, P, and Duffy blood groups either in the dominant simplex or dystrophic forms of epidermolysis bullosa (Table III).

Protocols for these families in respect of blood linkage markers are set out in Appendix I, and the associated diagrammatic pedigrees in Appendix II.

Discussion

These findings and the grouping of cases are similar to those of other authors. In the dominant families there was no skipping of a generation, but this phenomenon has been described by Gossage (1908) and Tilsley and Beard (1963) and is not surprising in view of the mildness of some manifestations. Everyone gets friction blisters at some time or other and it may be impossible to say whether such blisters have any special significance. Nippert and Fetter (1945) described cases of proneness to feet blisters after marching in soldiers, and individual susceptibilities varied: no doubt some of these cases were examples of epidermolysis bullosa (Cockayne).

TABLE III

LINKAGE SCORES FOR DOMINANT EPIDERMOLYSIS BULLOSA (SCORES BY PENROSE'S SIB-PAIR METHOD)

	Blood Groups				
	ABO	Rhesus	MNS	P	Duffy
<i>Families with dominant epidermolysis bullosa simplex</i>					
No. of sib pairs: n	69	68	37	61	58
Sum of scores: η SC	6.96	2.93	-2.79	-5.24	-6.67
Sum of information: η^2 SI	64.92	86.85	51.85	48.64	41.85
SC/ $\sqrt$ SI	0.86	0.31	-0.39	-0.75	-1.03
<i>Families with dominant epidermolysis bullosa dystrophica</i>					
No. of sib pairs: n	26	26	26	26	26
Sum of scores: η SC	-2.10	1.43	7.43	2.72	6.76
Sum of information: η^2 SI	2.79	6.02	20.36	19.01	26.54
SC/ $\sqrt$ SI	-1.26	0.58	1.65	0.62	1.31

None of the very severe recessive cases of the type epidermolysis bullosa hereditaria letalis (Herlitz, 1935) were encountered in this study. One obstetrician in the area had seen a fatal case in a newborn some years previously but the family could not be traced. Such cases determining early death must be very uncommon. In England and Wales deaths in the first year of life from all congenital skin disorders and pemphigus neonatorum average about 15 per million births. Epidermolysis bullosa might be mistaken occasionally for pemphigus neonatorum, and the total numbers of deaths due to pemphigus neonatorum and those due to congenital malformations of the skin are about equal. It seems most unlikely that epidermolysis bullosa would constitute more than one-fifth of these cases, and perhaps two or three per million births. Böök (1952), from 44,109 consecutive births, estimated the mutation rate of epidermolysis bullosa hereditaria letalis in Sweden as 5×10^{-8} . It is still uncertain that there is, as stated by Herlitz (1935), a distinct lethal form or that the recessive dystrophic form shows a continuous spectrum of severity at one end of which the condition is often fatal. Klunker (1963) and Muggler (1963) appear to subscribe to the latter view. Fox (1879) described a family with three severely affected children and one of them died at 6 days, while Coste, Piguet, and Civatte (1952) reported a family where there was a severely affected girl aged 8 years and her affected sister who had died in infancy.

As will be seen from Table I in the cases reported, no examples of involvement of teeth were encountered. Winstock (1962) considered that irregularity in the teeth in patients was most probably secondary to obliteration of the normal gingival tissue following the formation of bullae. No corneal or conjunctival changes such as those observed

by Cohen and Hopkins (1950) were seen, nor were there examples of the severe affection of the pharynx and oesophagus which may be found in the recessive group. Malignant changes in the skin as reported by Halpern (1947) and Rasponi (1950) were not observed. Moynahan (1963) reported marked improvement in six very severely affected patients of various ages after treatment with large doses of cortisone. He considered that it controlled the inflammatory process so that tissue damage and liability to blister formation were reduced. Leland and Hirschl (1954) reported a family where cortisone had been given to twin girls without any improvement.

Genetic Implications. There appears not to be a continuous spectrum of severity of dominant cases but rather it seems necessary to postulate different mutations to explain the distinct dystrophic and non-dystrophic forms. Within given families, ages of onset appear to vary little, though sufficient confidence cannot be put on the remembered ages to justify intrafamilial and interfamilial correlations. However, within a given family the condition appears invariably to be either dystrophic or simplex. That different mutations are involved is supported by histopathological findings: in the simplex form the blister forms in the epidermis, in the same way as friction blisters. In the dystrophic forms, both dominant and recessive, the site of blister formation is deeper. Roberts, Howell, Bramhall, and Reubner (1960) suggested that in the severe recessive form the primary defect was vesicular degeneration of the basal cells of the epidermis followed by cleavage at the dermo-epidermal junction. Electron-microscopy studies by Pearson and Spargo (1961) revealed disintegration of the basal and suprabasilar cells which the authors attributed to the release of a necrotizing

agent in the dermis and epidermis following local trauma, and to an inherent weakness in the cell structure. Engman and Mook (1906) considered that the condition was due to the absence or underdevelopment of the elastic fibres in the corium, and this was supported by Leoni (1950) and by Dorn (1957). However, Ebert and Slepian (1937) and Stritzler (1960) could not detect any abnormality of elastic tissues. Pearson (1962) suggested that in the recessive form an abnormal collagen was present or a collagenase-like substance was active. There does not appear to be any histopathological differentiation of recessive and dominant dystrophic types.

However, on the basis of clinical findings and histopathology we need to postulate two mutations to explain the findings and on genetic grounds we need a third to explain the two types of inheritance of the dystrophic form. We have no means of knowing whether any two or all three of these are alternative alleles, linked or non-linked autosomal mutations.

Haldane (1936) suggested that in the published data of families with recessive dystrophic epidermolysis bullosa there was evidence of partial sex-linkage. This is now thought to be unlikely on cytological grounds and as a result of more careful selection of pedigrees for analysis. In the two reported families there was no consanguinity and no evidence in the sibships of an undue number of either sex being affected. Thus no information has been contributed to support this hypothesis.

Summary

Examinations have been carried out in 28 families on 77 patients with epidermolysis bullosa. The patients were grouped according to the clinical findings and the mode of inheritance. There were 50 with dominant epidermolysis bullosa simplex and this included those patients previously diagnosed as having epidermolysis bullosa (Cockayne). Of the 27 patients with epidermolysis bullosa dystrophica, 21 were considered to have the dominant and 6 the recessive type.

Seven families with dominant epidermolysis bullosa were selected for linkage studies. Neither the simplex nor the dystrophic forms of epidermolysis bullosa showed evidence of linkage with ABO, Rhesus, MNS, P, or Duffy blood groups.

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APPENDIX I

Linkage Data for Dominant Epidermolysis Bullosa

Family No.	Pedigree No.	A† U	Sex	Age (yr.)	ABO	Rhesus	MN	S	Lu(a)	P	K	Le(a)	Le(b)	Fy(a)	Jk(a)
<i>Families with epidermolysis bullosa simplex</i>															
15	I 2	A	F	72	O	cDE/cde	MN	—	+	+	—	—	+	+	..
	II 1	U	M	48	A ₁	CDe/cDE	MN	—	..	+	—	—	+	+	..
	2	U	F	45	A ₁	cDE	N	—	..	+	—	—	+	+	..
	3	A	M	42	B	CDe/cDE	MN	+	..	+	—	—	+	+	..
	4	U	F	29	O	cde/cde	N	—	..	—	—	—	+	+	..
	5	A	F	39	B	CDe/cde	MN	..	..	+	—	—	+	+	..
	6	U	M	39	O	CDe/cDE	N	—	..	+	—	—	+	+	..
	III 4	A	F	7	O	CDe/cde	MN	—	—	—	—	—	+	+	..
	5	U	F	5	O	cDE/cde	MN	—	—	+	—	—	+	+	..
	6	U	M	3	O	cDE/cde	N	—	—	—	—	—	+	+	..
	7	U	F	1 ^{1/2}	B	cDE/cde	..	..	..	..	..	..	+	+	..
	8	U	F	3 ^{1/2}	B	cDE/cde	..	..	..	..	..	..	+	+	..
	9*	A	M	13	O	CDe/cDE	N	—	..	+	—	—	+	+	..
20	10	U	M	9	B	CDe/cde	N	..	..	—	—	—	+	+	..
	11	U	M	7	B	CDe/cDE	N	..	..	+	—	—	+	+	..
	12	U	M	4	B	CDe/CDe	MN	..	..	+	—	—	+	+	..
	13	U	M	2	O	CDe/CDe	MN	—	—	—	—	+	+	+	..
	III 1	U	M	62	O	CDe/CDe	MN	+	—	+	—	+	—	+	+
	IV 1	U	F	40	O	CDe/cde	MN	+	—	—	—	+	—	+	+
	3	A	M	37	O	CDe/cde	MN	+	+	—	—	+	—	+	+
	4	A	M	38	O	CDe/cde	MN	+	+	—	—	+	—	+	+
	6	A	M	31	O	CDe/cde	MN	+	+	—	—	+	—	+	+
	7	U	F	30	O	cDE/cde	MN	—	+	+	—	+	—	+	+
	V 3	U	M	10	O	CDe/cde	MN	+	+	—	—	+	—	+	+
	4	A	M	9	O	cde/cde	M	—	—	—	—	+	—	—	—
	5*	A	F	3	O	cde/cde	MN	—	—	—	—	+	—	—	—
27	7	A	F	5	O	CDe/cde or cDE/cde	MN	+	+	—	—	+	—	+	+
	9	U	F	2	O	CDe/cde	N	+	+	—	—	+	—	+	+
	II 4	A	M	55	O	CDe/cDE	M	—	—	+	+	—	+	—	+
	5	U	F	50	B	CDe/cde	N	..	..	—	—	+	—	+	..
	III 7	A	M	25	O	cDE/cde	MN	—	..	+	—	—	+	—	—
	9	A	F	22	O	cDE/cde	MN	—	..	+	—	—	+	—	—
	10	A	M	20	O	CDe/cDE	MN	—	—	+	—	+	—	+	+
	11	A	F	18	B	CDe/cde	MN	..	..	—	—	+	—	—	..
	12	A	F	18	B	cDE/cde	MN	..	..	—	—	+	—	—	..
	13	U	M	16	O	CDe/cDE	MN	—	—	—	+	—	+	—	+
	14*	A	F	7	O	cDE/cde	MN	—	—	+	—	—	+	—	+
28	II 1	A	M	59	O	CDe/cde	MN	—	+	—	—	—	+	—	+
	2	U	F	45	O	CDe/cde	MN	+	—	+	—	—	+	—	+
	3	A	F	57	O	cDE/cde	MN	+	—	+	—	—	+	—	+
	4	U	M	62	A ₁	CDe/cDE	MN	+	+	—	—	—	+	—	+
	5	A	M	52	O	CDe/cDE	MN	—	—	—	—	—	+	—	+
	6	U	F	41	A ₂	cde/cde	N	+	+	+	+	—	+	—	+
	7	A	F	49	O	CDe/cde	MN	+	—	—	—	—	+	—	+
	8	A	M	46	O	CDe/CDe	MN	+	—	—	—	—	+	—	+
	9	U	F	40	A ₁	CDe/cde	N	+	—	—	—	—	+	—	+
	III 1	U	M	45	O	CDe/CDe	MN	—	..	—	—	—	+	—	+
	2*	U	M	26	O	CDe/cde	MN	+	+	+	—	—	+	—	+
	3	A	F	24	O	cde/cde	N	+	+	+	—	—	+	—	+
	4	U	F	24	A	CDe/cDE	MN	+	+	+	+	—	+	—	+
	5	U	F	23	O	CDe/CDe	MN	+	+	+	—	—	+	—	+
	6	U	F	21	A ₁	CDe/cDE	MN	+	+	+	—	—	+	—	+
	7	A	F	15	A ₁	CDe/CDe	MN	+	+	+	—	—	+	—	+
	8	A	F	16	A ₂	cDE/cde	MN	—	+	—	—	—	+	—	+
	9	A	F	14	A ₂	CDe/cde	N	+	+	—	—	—	+	—	+
	10	U	F	18	A ₁	CDe/cde	N	+	+	—	—	—	+	—	+
	11	U	F	16	A ₁	CDe/cde	N	+	+	—	—	—	+	—	+
	IV 1	A	M	2	A	..	..	..	..	..	..	..	..	..	..
	2	U	M	3 ^{1/2}	A	..	..	..	..	..	..	..	..	..	..

APPENDIX I—continued

Family No.	Pedigree No.	A† U	Sex	Age (yr.)	ABO	Rhesus	MN	S	Lu(a)	P	K	Le(a)	Le(b)	Fy(a)	Jk(a)
<i>Families with epidermolysis bullosa dystrophica</i>															
23	I 3	A	M	68	O	CDe/cde	N	+	—	+	—	—	—	—	+
	II 1	U	M	38	B	cde/cde	MN	+	+	—	—	+	—	+	+
	2	A	F	43	O	CDe/CDe	MN	+	—	—	—	—	—	+	+
	III 1	A	M	15	O	CDe/cde	MN	+	—	—	—	—	—	+	+
	2	U	M	8	O	CDe/cde	MN	+	—	—	—	—	—	+	+
29	3*	A	F	6	O	CDe/cde	MN	—	—	—	—	+	—	—	+
	III 1	U	M	61	A ₁	CDe/cDE	MN	—	—	+	+	—	+	+	+
	IV 2	A	F	38	A ₁	CDe/cDE	MN	+	+	+	+	—	+	+	+
	3	U	M	40	O	CDe/cDE	MN	—	—	+	+	+	+	+	+
	4	U	M	37	A ₁	CDe/cDE	MN	—	—	+	+	+	+	+	+
	5	U	M	31	A ₁	CDe/cDE	MN	+	—	+	+	—	+	+	+
	6	A	F	29	O	CDe/CDe	MN	+	—	+	+	+	+	+	+
	8	U	F	28	A ₁	CDe/cDE	MN	—	—	+	+	+	+	+	+
	10	A	F	21	A ₁	CDe/cDE	MN	+	—	+	+	+	+	+	+
	11	U	M	28	O	CDe/CDe	N	—	—	+	+	+	+	+	+
	V 1†	A	F	13	B	CDe/cDE	MN	+	+	+	+	+	+	+	+
	2	U	M	8	O	CDe/cDE	N	—	—	—	+	+	+	+	+
	3	U	F	6	O	CDe/cDE	MN	—	—	+	+	+	+	+	+
	4	U	F	5	O	CDe/cDE	MN	+	—	+	+	+	+	+	+
	5	U	F	4	A ₁	CDe/cDE	MN	+	—	+	+	+	+	+	+
	10*	A	F	7	A ₁	CDe/cDE	MN	+	—	+	+	+	+	+	+
	11	A	F	4	A ₁	CDe/cDE	MN	+	—	+	+	+	+	+	+
	12	A	M	3	A ₁	CDe/cDE	MN	—	—	+	+	+	+	+	+
	13	A	F	5	A ₁	CDe/cDE	N	—	—	+	+	+	+	+	+
30	I 2	A	M	54	O	CDe/cde	MN	—	+	+	—	+	—	—	+
	3	U	F	53	O	cde/cde	MN	—	—	+	—	—	—	+	+
	II 2*	U	M	24	O	cde/cde	MN	—	+	—	—	—	—	+	+
	3	U	M	27	A ₁	CDe/cDE	MN	+	—	+	—	+	—	—	+
	4	U	F	20	O	CDe/cde	N	—	—	+	—	—	—	+	+
III	5	U	M	16	O	cde/cde	MN	—	+	+	—	+	—	—	+
	1	U	M	1	A ₁	CDe/cDE	MN	+	—	+	—	+	—	—	+

* Propositus.
† Epidermolysis bullosa: A, affected; U, unaffected.
‡ Blood grouping shows that she is illegitimate.
Note. S is phenotype S + or —; Lu(a) is Lutheran phenotype Lu(a+) or Lu(a—); P is P phenotype P + or —; K is Kell phenotype K + or —; Le(a) is Lewis phenotype Le(a+) or Le(a—); Le(b) is Lewis phenotype Le(b+) or Le(b—); Fy(a) is Duffy phenotype Fy(a+) or Fy(a—); Jk(a) is Kidd phenotype Jk(a+) or Jk(a—).
Two dots (..) = not tested.

APPENDIX II

Pedigrees of 7 Families with Dominant Epidermolysis Bullosa