Inherited epidermolysis bullosa
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Abstract
Inherited epidermolysis bullosa (EB) encompasses a number of disorders characterized by recurrent blister formation as the result of structural fragility within the skin and selected other tissues. All types and subtypes of EB are rare; the overall incidence and prevalence of the disease within the United States is approximately 19 per one million live births and 8 per one million population, respectively. Clinical manifestations range widely, from localized blistering of the hands and feet to generalized blistering of the skin and oral cavity, and injury to many internal organs. Each EB subtype is known to arise from mutations within the genes encoding for several different proteins, each of which is intimately involved in the maintenance of keratinocyte structural stability or adhesion of the keratinocyte to the underlying dermis. EB is best diagnosed and subclassified by the collective findings obtained via detailed personal and family history, in concert with the results of immunofluorescence antigenic mapping, transmission electron microscopy, and in some cases, by DNA analysis. Optimal patient management requires a multidisciplinary approach, and revolves around the protection of susceptible tissues against trauma, use of sophisticated wound care dressings, aggressive nutritional support, and early medical or surgical interventions to correct whenever possible the extracutaneous complications. Prognosis varies considerably and is based on both EB subtype and the overall health of the patient.
disease; and (3) inclusion of the laryngo-onycho-cutaneous syndrome (LOC; previously called Shabbir's syndrome) [8,9], given its shared molecular target with that of JEB [10].

Epidemiology

Estimates of prevalence and incidence of EB have been attempted by different sampling techniques in a number of populations worldwide, but the most rigorously obtained ones are derived from the National EB Registry (NEBR), a cross-sectional and longitudinal epidemiological study of EB patients across the entire continental United States. Over its 16 years (1986-2002) of formal funding by the National Institutes of Health, nearly 3,300 EB patients were identified, enrolled, classified, clinically characterized, and followed for outcomes. Among this robust study population, the prevalence and incidence of EB was estimated as approximately 8 per one million population and 19 per one million live births, in 1990 and 1986-1990, respectively [11-13]. These data were then used to estimate carrier frequencies for EB within the United States [14]. The NEBR prevalence and incidence estimates are very similar to most of those reported elsewhere (the largest cohort of which is the Italian EB Registry [15]) [16-18], many of which used less rigorous epidemiological sampling methods. The overall consistency of these data in different parts of the world suggests that the epidemiological data that have been derived by the NEBR can indeed be generalized worldwide. Of note, a greater prevalence of EBS has been reported from Scotland [19]. It is unclear whether this reflects possible greater accessibility of EBS patients for identification and recruitment in the Scottish Registry or the presence of some underlying genetic differences which might distinguish the Scottish EB population from those in other geographic regions. For example, the American NEBR data on EBS are based on the actual findings of the NEBR study population [11]. Revised estimates of both prevalence and incidence in the United States, based on assumptions of incomplete capture of EBS cases, have been published in greater detail in the peer-reviewed monograph which was based on the NEBR database [11]. Given how relatively mild the disease activity usually is in localized EBS, it is indeed possible that our prevalence and incidence data on American EBS patients may be an underestimate if our enrollment of EBS patients had been discordantly low, although our overall data so closely match those from Italy that this hypothesis is probably incorrect.

An important demographic finding among the NEBR study population was the lack of any EB type or subtype predilection by gender or ethnicity. In particular, when

| Major EB Types       | Level of Blister Formation                  |
|----------------------|---------------------------------------------|
| EB simplex           | Intraepidermal                              |
| Junctional EB        | Intra-lamina lucida                         |
| Dystrophic EB        | Sub-lamina densa                            |
| Kindler syndrome     | Multiple levels (intra-lamina lucida and sub-lamina densa) |

Table 1: EB synonyms

| Name                                          | Synonym(s)                                      |
|------------------------------------------------|-------------------------------------------------|
| Inherited EB                                  | EB hereditaria                                  |
| EB simplex, localized                         | EB simplex, Weber-Cockayne; EB simplex of palms and soles |
| EB simplex, Dowling-Meara                     | EB (simplex) herpetiformis                      |
| EB simplex, generalized non-Dowling-Meara      | EB simplex, Koebner; EB simplex, generalized other |
| Junctional EB                                 | EB atrophicans                                  |
| JEB, Herlitz                                  | JEB generalisata gravis                         |
| JEB, non-Herlitz                              | JEB generalisata mitis                         |
| Dystrophic EB (DEB)                           | EB dystrophica                                  |
| Dominant dystrophic EB (DDEB)                 | DDEB, Pasini and Cockayne-Touraine variants     |
| Recessive dystrophic EB (RDEB), severe generalized | RDEB, Hallopeau-Siemens; RDEB generalisata gravis |
| RDEB, generalized other                       | RDEB, non-Hallopeau-Siemens; RDEB generalisata mitis |
| EB with congenital localized atrophy of skin  | Bart’s syndrome                                 |

Table 2: Level of blister formation in each major EB type
allowances were made for ethnic differences in access to specialty care within the United States, the overall distribution of NEBR subjects closely resembled that of the general American population [20].

As anticipated from previous anecdotal experiences worldwide, the majority of EB patients in the NEBR cohort had some type of EB simplex [11]. Of these, the majority had the localized subtype. As also expected, the majority of patients with generalized junctional EB (JEB) had the less severe (non-Herlitz) subtype, and the majority of patients with generalized recessive dystrophic EB (RDEB) had the clinically less severe (non-Hallopeau-Siemens) subtype of this disease.

Clinical description

General considerations [2]
The hallmark cutaneous features of inherited EB, in addition to mechanically fragile skin and easy inducibility of blisters (Figure 1) or erosions, include some or all of the following: milia (tiny firm white papules, resembling cysts or pustules) (Figure 2), nail dystrophy or absence, and scarring (usually atrophic). Additionally useful findings, if present, include exuberant granulation tissue (peri-orificial; axillary vaults; nape of the neck; lumbosacral spine; periungual and proximal nail folds), localized or confluent keratoderma of the palms and soles, and dyspigmentation (postinflammatory hypo- or hyperpigmentation; mottled or reticulate hyperpigmentation). Infrequently seen and extremely nonspecific cutaneous findings include decreased or absent hair, albopapuloid lesions (flesh-colored or hypopigmented papules, usually arising on the lower trunk), and hypo- or hyperhidrosis [21].

Several factors must be considered when attempting to use cutaneous findings as surrogate diagnostic markers. First, the presence or absence of one or more findings may be age-dependent [22]. That is, not all of these skin findings are necessarily seen in neonates or infants. For example, scarring, nail dystrophy, milia, and exuberant granulation tissue may develop only after several months or even years of life. As such, their absence cannot be reliably used for diagnosis during that window of time (i.e., early infancy) when classification and subclassification are most needed [22]. Similarly, exuberant granulation tissue, the most pathognomonic skin finding in EB, which

| EB type                          | Major EB subtype                  | Level of cleavage | Associated ultrastructural findings                                                                 |
|---------------------------------|-----------------------------------|-------------------|-----------------------------------------------------------------------------------------------------|
| EB simplex (suprabasal)         | EB simplex superficialis           | subcorneal        | ---                                                                                                   |
|                                 | lethal acantholytic EB            | suprabasal        | acantholysis; perinuclear retraction of keratin filaments                                             |
|                                 | EBS, plakophilin deficiency       | mid-epidermis     | perinuclear retraction of keratin filaments; small suprabasal desmosomes                             |
| EBS (basal)                     | EBS, localized                    | basal keratinocyte| ---                                                                                                   |
|                                 | EBS, Dowling-Meara                | basal keratinocyte| clumped keratin filaments                                                                           |
|                                 | EBS, generalized other            | basal keratinocyte| ---                                                                                                   |
|                                 | EBS, autosomal recessive          | basal keratinocyte| absent or reduced keratin filaments within basal keratinocytes                                       |
| Junctional EB                   | JEB, Herlitz                      | intra-lamina lucida| markedly reduced or absent hemidesmosomes; absent subbasal dense plates; absent anchoring filaments |
|                                 | JEB, non-Herlitz                  | intra-lamina lucida| hemidesmosomes may be normal or reduced in size and number                                           |
|                                 | JEB with pyloric atresia          | intra-lamina lucida| small hemidesmosome plaques with attenuated subbasal dense plates                                      |
| Dominant dystrophic EB          | DDEB, generalized                 | sub-lamina densa  | normal or reduced numbers of anchoring fibrils                                                       |
|                                 | DDEB, bullous dermolysis of the newborn | sub-lamina densa | electron-dense stellate shaped bodies within basal keratinocytes; reduced numbers of anchoring fibrils |
| Recessive dystrophic EB         | RDEB, severe generalized          | sub-lamina densa  | absent or rudimentary appearing anchoring fibrils                                                    |
|                                 | RDEB, generalized other (generalized mitis) | sub-lamina densa | reduced or rudimentary appearing anchoring fibrils                                                  |
is seen almost exclusively in the Herlitz subtype of generalized JEB, may completely resolve spontaneously in rare patients during adulthood. Second, some findings (such as albopapuloid lesions or aplasia cutis) may arise in more than one EB type or subtype, making them insufficiently specific to be reliably used as diagnostic tools [21]. Indeed, when sensitivity and specificity analyses were performed on the robust database of the NEBR, the only cutaneous finding reaching 90% in both sensitivity and specificity as a surrogate diagnostic marker (even when up to three findings were considered in combination) was exuberant granulation tissue, emphasizing the inherent risks associated with relying too heavily solely on the presence or absence of EB-associated skin findings [22].

All types and subtypes of inherited EB are associated with mechanically fragile skin. This can be induced by light lateral or rotary traction to the skin. In general, skin from patients with JEB and RDEB is much more fragile than that of EBS patients. Although most EB patients usually present with intact blisters, erosions may instead be the overriding finding in patients having one of the more superficial (i.e., suprabasal) EBS subtypes [3]. Skin fragility in EB is characteristically worsened in warm weather or warm living environments; hence the value of air-conditioning for families with affected children. The one exception to this observation, which is seen in only a subset of EBS-DM patients, is a temporary reduction of blistering during periods of high fever. Of practical importance, a history of seasonally dependent (i.e., summertime) blistering is more often elicited in EB patients having milder or more localized types or subtypes of the disease, especially those with EBS, since the most severely affected patients (particularly those with generalized JEB and RDEB) have such continuous generalized blistering that any influence by temperature is clinically negligible.

Potentially any extracutaneous tissue which is lined or surfaced by epithelium may be injured in EB [23-25]. In general, the more severe and widely distributed the blistering on the skin is, the more likely it is for multiple extracutaneous sites to also become involved. As is the case with cutaneous findings, these extracutaneous complications are also age-dependent, with time of onset and cumulative risk of occurrence highly dependent on the EB subtype that is present. Examples of the cumulative risks for the most important extracutaneous complications will be reviewed in detail elsewhere in the context of specific EB subtypes. As will also be discussed subsequently, other non-epithelial organs or tissues may also

| Common antigens | Abnormal staining in | Typical pattern of staining |
|-----------------|----------------------|-----------------------------|
| Keratin 5       | ---                  | normal filamentous network within keratinocytes |
| Keratin 14      | EBS, autosomal recessive | absent or markedly reduced staining of filaments within keratinocytes |
| Laminin-332 (laminin-5) | JEB-H | absent or markedly reduced staining along the DEJ |
|                 | JEB-nH *             | reduced staining along the DEJ |
| Type XVII collagen | JEB-nH *         | reduced or absent staining along the DEJ |
| Type VII collagen | RDEB, severe generalized | usually absent staining along the DEJ |
|                 | RDEB, generalized other | reduced staining along the DEJ |
|                 | RDEB, inversa         | variable staining along the DEJ |
|                 | Dystrophic EB-BDN (only during periods of active blistering) | granular staining within basal and lower suprabasal keratinocytes; absent or markedly reduced staining along the DEJ |
| Plectin         | EBS with muscular dystrophy; EBS with pyloric atresia; EBS-Ogna | absent or reduced staining along the DEJ; absent or reduced staining along the DEJ; reduced staining along the DEJ |
| α6β4 integrin   | JEB with pyloric atresia; EBS with pyloric atresia | absent or reduced staining along the DEJ; absent or reduced staining along the DEJ |
| Kindlin-1       | Kindler syndrome     | absent or reduced staining along the DEJ |

DEJ = dermoepidermal junction

* The majority of patients with JEB-nH have mutations in one of the three genes encoding for laminin-332, rather than within the gene for type XVII collagen. Of note, there are usually no phenotypic differences in these two antigenically distinct JEB-nH groups.

Modified from Fine J-D et al, 2008 (reference [3]); refer to that reference for less frequent findings.
Table 5: Major EB subtypes and their targeted proteins (per the 2008 international consensus report)

| Major EB Type               | Major EB Subtypes                                      | Targeted Protein(s)                      |
|-----------------------------|--------------------------------------------------------|------------------------------------------|
| EB simplex (EBS)            | suprabasal subtypes                                    |                                          |
|                            | lethal acantholytic EBS                                | desmoplakin                              |
|                            | plakophilin-1 deficiency                               | plakophilin-1                            |
|                            | EBS superficialis (EBS5)                               | ?                                       |
|                            | basal subtypes                                         |                                          |
|                            | EBS, localized (EBS-loc)                               | K5, K14                                  |
|                            | EBS, Dowling-Meara (EBS-DM)                            | K5, K14                                  |
|                            | EBS, other generalized (EBS-,gen nDM)                  | K5, K14                                  |
|                            | EBS with mottled pigmentation (EBS-MP)                 | K5                                       |
|                            | EBS with muscular dystrophy (EBS-MD)                   | plectin                                  |
|                            | EBS with pyloric atresia (EBS-PA)                      | plectin; α6β4 integrin                   |
|                            | EBS, autosomal recessive (EBS-AR)                      | K14                                      |
|                            | EBS, Ogna (EBS-Og)                                     | plectin                                  |
|                            | EBS, migratory circinate (EBS-migr)                    | K5                                       |
| Junctional EB (JEB)         | JEB, Herlitz (JEB-H)                                   | laminin-332                              |
|                            | JEB, generalized non-Herlitz (JEB-nH gen)              | laminin-332; type XVII collagen          |
|                            | JEB, localized non-Herlitz (JEB-nH loc)                | type XVII collagen                       |
|                            | JEB with pyloric atresia (JEB-PA)                      | α6β4 integrin                            |
|                            | JEB, inversa (JEB-I)                                   | laminin-332                              |
|                            | JEB, late onset (JEB-lo)                               | ?                                       |
|                            | LOC syndrome                                           | laminin-332 α3 chain                     |
| Dominant dystrophic EB (DDEB)| DDEB, generalized (DDEB-gen)                        | type VII collagen                        |
|                            | DDEB, acral (DDEB-ac)                                  | type VII collagen                        |
|                            | DDEB, pretibial (DDEB-Pt)                              | type VII collagen                        |
|                            | DDEB, pruriginosa (DDEB-Pr)                            | type VII collagen                        |
|                            | DDEB, nails only (DDEB-na)                             | type VII collagen                        |
|                            | DDEB, bullous dermolysis of newborn (DDEB-BDN)         | type VII collagen                        |
| Recessive dystrophic EB (RDEB)| RDEB, severe generalized (RDEB-sev gen)               | type VII collagen                        |
|                            | RDEB, generalized other (RDEB, generalized mitis) (RDEB-O)| type VII collagen                   |
|                            | RDEB, inversa (RDEB-I)                                 | type VII collagen                        |
|                            | RDEB, pretibial (RDEB-Pt)                              | type VII collagen                        |
|                            | RDEB, pruriginosa (RDEB-Pr)                            | type VII collagen                        |
|                            | RDEB, centripetalis (RDEB-Ce)                          | type VII collagen                        |
|                            | RDEB, bullous dermolysis of newborn (RDEB-BDN)         | type VII collagen                        |
| Kindler syndrome            |                                                         | kindlin-1                                |

Modified from Fine JD et al (reference [3])
be involved in selected EB subtypes. For example, enamel hypoplasia [26] is seen exclusively in all subtypes of JEB (and is therefore a highly useful diagnostic finding), and muscular dystrophy (either congenital or late onset) may accompany one specific subtype of EBS. Some other organs, for example, the heart and kidney, may also become secondarily injured in severely affected EB patients.

When counseling a family with an affected child, it is important to realize that considerable variability in the frequency and severity of extracutaneous complications may be seen within not only a single major EB subtype but even within a kindred. The risk and time of onset of occurrence of these complications may vary considerably from one EB subtype to another. Some EB types and subtypes are particularly at risk for premature death from one or more causes. Finally, genotype-phenotype correlation, with the exception of EBS, is rather weak [3].

**EB simplex**

As discussed in much greater detail within the 2008 consensus report [3], there is a wide range of cutaneous findings among the many EBS subtypes. With only three rare exceptions (Table 5), blisters arise within the basal layer of the epidermis in patients with EBS. Onset of disease activity in EBS is usually at or shortly after birth, although patients with localized EBS may not develop blistering until late childhood or even early adulthood. As a general rule, far less scarring, milia formation, and nail dystrophy are seen in EBS, as compared to JEB and DEB, although even the combination of all three of these clinical findings, when used as a diagnostic test to distinguish EBS from all other EB types, failed to provide both sensitivity and specificity of > 90% [21].

The most common type of EB, as well as the most common subtype of EBS, is *localized EBS*, formerly known as Weber-Cockayne disease. Among the National EB Registry population, half of all participants had EBS; of these, two-thirds had localized EBS [20]. The usual distribution of blisters in these patients is on the palms and soles (Figure 3), although any other skin surface may also blister if sufficiently traumatized. Milia, scarring, and nail dystrophy are uncommon to rare skin findings in all forms of EBS, with the lowest frequency noted in localized EBS. The only common extracutaneous finding in localized EBS, localized intraoral erosions or blisters, tends to be asymptomatic, occurs in about one-third of these patients, and usually is seen only during infancy [27,28].

There are several subtypes of more generalized EBS. The most noteworthy one, *EBS-Dowling Meara (DM)* [29], is frequently associated with marked morbidity and, in a minority of patients, may result in death during early infancy. Its hallmark feature is the presence of intact vesicles or small blisters in grouped or arcuate configuration (Figure 4). Such herpes simplex-like clustering of lesions explains why this entity was originally named EB herpetiformis, although there is no true association between this disease and either herpetic infection or the autoimmune bullous disease, dermatitis herpetiformis. By late childhood, most patients with EBS-DM develop confluent thickening and hyperkeratosis (“keratoderma”) of the palms and soles which may partially resolve in some patients during mid- to late-adulthood. Although not a universal finding, some patients with EBS-DM may...
improve when febrile, which is paradoxical, since warmer weather exacerbates disease activity in all EB patients. The reason for such a phenomenon is unknown. The most notable extracutaneous complication in EBS, and one that is seen in only rare patients with EBS-DM, is tracheolaryngeal compromise, mimicking that which arises in both major subtypes of JEB [30,31]. There is also a markedly increased risk of developing basal cell carcinomas by mid-adulthood (cumulative risk of 44% by age 55) [32], a finding seen in EB only among patients with EBS-DM.

Another subtype of generalized EBS ("EBS generalized other" or non-Dowling-Meara generalized EBS), formerly named EBS-Koebner (EBS-K), is characterized by non-herpetiform blisters and erosions arising on any skin surface [33]. Of note, these blisters tend to spare the palms and soles, distinguishing them from patients with localized EBS. The frequency of milia, scarring, and nail dystrophy is intermediate between that of localized EBS and EBS-DM, and extracutaneous findings, other than occasional intraoral blistering, are rare. Given the considerable overlap between EBS-K and localized EBS within some kindreds, some experts prefer to group both subtypes together.

Other clinically striking but rare basal EB subtypes include EBS with mottled pigmentation (EBS-MP) [34,35], EBS with muscular dystrophy (EBS-MD) [36,37], autosomal recessive EBS [38], EBS with circinate migratory blistering [39], and EBS-Ogna [40,41], the latter of which is associated with easy bruisability, hemorrhagic blistering, and marked nail deformity (onychogryphosis) [3]. From a prognostic point of view, immunohistochemical recognition of EBS-MD in infancy is particularly important, since in some patients the associated muscular dystrophy may not become apparent until later in childhood or early adulthood.

**Junctional EB**

There is only one clinical finding that is characteristic of all subtypes of JEB -- the presence of enamel hypoplasia, manifested as localized or more extensive thimble-like pitting of some or all of the tooth surfaces (Figure 5) [26,42]. It is therefore an extremely useful clinical finding, although it cannot be used as a diagnostic tool until after the primary teeth have erupted.

There are two major JEB subtypes. The more severe one, JEB-Herlitz (JEB-H), is present at birth and involves all skin surfaces [43]. Approximately 20% of all JEB patients within the United States have this phenotype [11]. An essentially pathognomonic finding is exuberant granulation tissue (Figure 6), which usually arises within the first several months to one to two years of life. This may involve not only the skin but also the upper airway. Moderate to severe intraoral blistering is invariably present, with some eventual narrowing of the opening of the mouth ("microstomia") and reduced extension of the tongue ("ankyloglossia"), although these findings are not as pronounced as is observed in severe generalized RDEB [27]. Rather profound growth retardation and multifactorial anemia are the norms in JEB-H [25]. Many other organs may be involved, including but not restricted to the esophagus (strictures) [44], external eye (corneal blisters, erosions, and scarring; ectropion formation) [45],
upper airway (strictures and occlusion) [30], and genito-
urinary tract [46]. Among JEB-H children, for example,
the cumulative risk of laryngeal stenosis or stricture is
40% by age 6 [30]. The highest risk of infant mortality
among EB neonates, infants, and young children occurs
in JEB-H, and is most often the result of sepsis, failure to
thrive, or tracheolaryngeal obstruction (the latter usually
secondary to severe progressive airway stenosis within or
above the level of the vocal cords) [47]. Indeed, as of Janu-
ary 1, 2002, over half of all JEB-H patients enrolled in the
NEBR had died within the first two years of life.
Squamous cell carcinomas may also arise in a minority of
JEB-H patients (cumulative risk of 18% by age 25) [32].

The most common JEB subtype, comprising nearly 80%
of the American JEB population, is non-Herlitz JEB (JEB-
nH), a generalized disorder characterized by the presence
of blistering, atrophic scarring, and nail dystrophy or
absence. It, too, is usually clinically apparent at birth.
Postinflammatory hypopigmentation or depigmentation
may be striking in some JEB-nH patients. A prominent
feature described among the original Tyrolean kindred
was scarring alopecia of the scalp [48], although experi-
ence in other populations has shown that this is not a uni-
versal finding among JEB-nH patients. The cumulative
risk of upper airway occlusion in JEB-nH (13% by age 9) is
lower than that observed in JEB-H [30] although the risk
of death among those JEB-nH patients with this complica-
tion is essentially the same. The frequencies of other
extracutaneous complications, including severe anemia
and growth retardation, however, are far lower among
JEB-nH than JEB-H patients, as is the risk of premature
death from non-airway-related complications [47].

A rare but clinically important JEB subtype, inverse JEB,
is associated with rather severe blistering and erosions
confined to intertriginous skin sites, esophagus, and
vagina [3].

JEB with pyloric atresia presents with generalized blis-
tering at birth and congenital atresia of the pylorus (and
rarely of other portions of the gastrointestinal tract)
[3,49]. This latter disorder is associated with a significant
risk of congenital anomalies of the genitourinary tract
and infantile or neonatal death. It should be noted that
rare patients with identical phenotypes have been shown
to have intraepidermal rather than intra-lamina lucida
 blister formation, necessitating their inclusion among the
rarer subtypes of EBS rather than JEB.

The LOC syndrome is characterized by localized blis-
tering and scarring, particularly on the face and neck, in
association with upper airway disease activity and nail
anomalies [8,9]. Characteristic cutaneous findings are
erosions and granulation tissue. The conjunctiva is
involved and enamel hypoplasia is present.

Dystrophic EB

Dystrophic EB (DEB) is separated into two major types,
based on the mode of transmission (autosomal dominant
versus autosomal recessive). As noted in Table 5, DEB
patients are further subdivided by clinical phenotype and
severity of disease [3].

Dominant dystrophic EB

By convention, all patients with generalized dominant
DEB (DDEB) are now grouped together. Although, in the
past, two DDEB subtypes, Pasini [50] and Cockayne-Tou-
raine DDEB [51], were considered to be different dis-
eases, more recent studies have failed to confirm either
the specificity of albopapuloid lesions or differences in
genotype between these two putatively distinct DDEB
subtypes [3]. The prototypic DDEB patient has general-
ized blistering at birth which, with time, is associated
with milia, atrophic (or less commonly, hypertrophic)
scarring (Figures 7 and 8), and nail dystrophy (Figure 9).
Recurrent esophageal blistering and erosions, leading to
progressive dysphagia secondary to esophageal stricture
formation, is common among these patients [44]. In con-
trast to severe generalized RDEB and JEB-H, however,
failure to thrive, growth retardation, severe anemia, early infant mortality, and risk of squamous cell carcinoma are not characteristic features of DDEB [24,25,47].

There are a number of less common DDEB subtypes, as listed in Table 5. A rare localized variant, acral DDEB, is characterized by cutaneous involvement confined primarily to the hands and feet. Of note, pseudosyndactyly is not a feature of this entity.

Pretibial DDEB, as the name implies, almost exclusively involves the anterior lower legs [52,53]. Individual lesions, which tend to be papular or plaque-like, are oftentimes somewhat violaceous, suggesting the clinical diagnosis of lichen planus. Bullae and scarring are also present. Dystrophy of both fingernails and toenails is characteristic; in contrast to lichen planus, these nail changes do not include pterygium formation.

DDEB pruriginosa is a more generalized subtype of DDEB which is characterized by severe, if not intractable, pruritus [54]. Bullous dermolysis of the newborn (BDN) is a subtype of dystrophic EB which is usually transmitted in an autosomal dominant manner [55]. It, like other generalized forms of EB, presents at or shortly after birth and may be accompanied by focal atrophic scarring. In contrast to all other types and subtypes of EB, disease activity usually ceases within the first 6 to 24 months of life.

A rare finding associated with EB and arising on one or more extremities, congenital localized absence of skin (CLAS) (Figure 10), was originally observed within a large kindred with autosomal dominant transmission of blistering; this family was later proven to have DDEB [56,57]. Referred to as Bart’s syndrome and once believed to be a distinct entity, it is now known that CLAS may arise in EBS, JEB, and RDEB, as well as in DDEB. As such, the eponym is no longer used and the condition is no longer deemed to be a separate EB subtype [5].

Recessive dystrophic EB

There are three main subtypes of RDEB -- severe generalized RDEB (formerly named Hallopeau-Siemens RDEB), non-Hallopeau-Siemens RDEB, and inverse RDEB. Each has its onset at birth. The most severe subtype, severe generalized RDEB, is clearly one of the most devastating multiorgan genetically transmitted diseases of mankind. Prototypic findings include generalized blistering at birth, progressive and oftentimes mutilating scarring of the skin, corneal blisters or scarring [45], profound growth retardation [44], multifactorial anemia, failure to thrive (less common than in JEB-H), esophageal strictures [44], and debilitating hand and foot deformities ("mitten deformities"; pseudosyndactyly) (Figures 11 and 12) [58]. Two
of these extracutaneous complications, esophageal strictures and pseudosyndactyly, are of particular importance, since they occur early in childhood and continue to negatively impact on the functionality of these patients throughout life. About 10% and 90% of all of these patients will develop symptomatic esophageal stricturing by ages 2 and 35, respectively [44]. Similarly, about 30% of severe generalized RDEB patients have signs of pseudosyndactyly as early as 2 years of age and virtually 100% will have developed this by age 20 [58].

Severe ankyloglossia and microstomia are the norm in severe generalized RDEB, and contribute to the markedly impaired oral intake of solid foods. Although secondary caries occur, no primary enamel defects exist in any type or subtype of dystrophic EB.

Chronic renal failure, the result of poststreptococcal glomerulonephritis or renal amyloidosis, occurs within this RDEB subtype, and may eventually lead to death in about 12% [59]. A low but real risk of potentially fatal dilated cardiomyopathy (4.5% cumulative risk by age 20, 30% of whom eventually die of this complication) exists in patients with severe generalized RDEB. Although the cause is unproven, data suggest the possibility that this may result from a micronutrient deficiency (carnitine; selenium) or chronic iron overload [60].

Although the risk of infantile death from any cause is low in RDEB, nearly all patients with severe generalized RDEB will develop at least one cutaneous squamous cell carcinoma (arising as early as within the second decade of life), and most (about 87% by age 45) will then die of metastatic squamous cell carcinoma within five years of the time of diagnosis of the first squamous cell carcinoma, despite apparent complete surgical removal of each primary carcinoma [32]. Rare children with severe generalized RDEB are also at risk of developing malignant melanoma (cumulative risk of 2.5% by age 12) although none of the latter has resulted in metastasis [32].

A more common RDEB subtype, formerly known as non-Hallopeau-Siemens RDEB (and probably best referred to as generalized mitis RDEB), has similar but less severe cutaneous involvement and a much lower risk of esophageal strictures, corneal injury, or hand or foot deformities. Growth retardation and anemia are extremely uncommon. However, these patients still have a significant risk of developing squamous cell carcinomas (47.5% by age 65), although the risk of death from metastases (60% by age 65) is lower than that which is seen in severe generalized RDEB [32].

A rare subtype of RDEB, inverse RDEB, is characterized by blistering and erosions which are primarily confined to
intertriginous skin sites, the base of the neck, the uppermost back, and the lumbosacral area. Patients with this subtype are particularly prone to develop severe blistering within the oral cavity, esophagus, and the lowermost portion of the genitourinary tract. Debilitating strictures may eventually develop within the esophagus (cumulative risks of 10% and 90% by ages 5 and 30, respectively) [44] and vagina. These strictures may be extremely severe, markedly impairing intake of nutrients and normal sexual functionality. Although squamous cell carcinomas may also arise in these patients, the cumulative risk (23% by age 45) is much lower than that which is seen in either of the two generalized subtypes of RDEB [32].

Bullous dermolysis of the newborn may rarely be transmitted as a severe autosomal recessive disease. In the setting of this mode of transmission, it may prove fatal within early infancy. Other rare RDEB subtypes include pretilial RDEB, RDEB pruriginosa, and RDEB centripetalis [61], the latter of which is characterized by cutaneous disease activity which begins acrally and then progressively spreads toward the trunk over decades.

**Kindler syndrome**

Kindler syndrome is characterized by generalized blistering at birth and the later development of characteristic poikilodermatous pigmentation and photosensitivity. Skin findings may include atrophic scarring and nail dysplasia. EBS-SS and its variants are known to arise as the result of mutations in the genes for plakophilin-1 and desmoplakin, respectively. The molecular etiology of EBS superficialis (EBSS) is still unclear although one family previously diagnosed with this was later shown to have a type VII collagen mutation similar to those seen in DDEB [64]. In support of EBSS being a distinctive entity, however, is the lack of any detectable type VII collagen mutation in the original published proband (unpublished data, 2009).

JEB-H results from severe mutations within any of the three genes which encode for the three-chained adhesion molecule, laminin-332 (previously named laminin-5). The presence of mutational hotspots with this disease facilitates rapid DNA screening in many patients. The majority of JEB-nH patients have less severe mutations within the same targeted genes, although a minority have mutations instead within the gene for plectin. A rare autosomal recessive form of EBS is known to result from mutations in the keratin 5 or keratin 14 gene. EBS with pyloric atresia is caused by mutations either within the gene for plectin or the genes for the heterodimeric transmembrane protein, α6β4 integrin. Two suprabasal subtypes of EBS -- plakophilin deficiency [62] and lethal acantholytic EB [63] -- are known to arise as the result of mutations in the genes for plakophilin-1 and desmoplakin, respectively. The molecular etiology of EBS superficialis (EBSS) is still unclear although one family previously diagnosed with this was later shown to have a type VII collagen mutation similar to those seen in DDEB [64]. In support of EBSS being a distinctive entity, however, is the lack of any detectable type VII collagen mutation in the original published proband (unpublished data, 2009).

**Etiopathogenesis**

**Genetics**

Inherited EB is transmitted as either an autosomal dominant or autosomal recessive disease, depending on EB type and subtype. As noted elsewhere, most EB phenotypes have only one mode of genetic transmission. Of importance, spontaneous mutations for autosomal dominant disease are not uncommon in EBS but account for only the minority of cases of DEB lacking a known family history for the disease. Incomplete penetrance has been documented only rarely in autosomal dominant EB kindreds.

**Molecular basis of disease**

Inherited EB has been shown to result from mutations in any of several structural proteins normally present within the keratinocyte or the skin basement membrane zone ("dermoepidermal junction") [3]. In general, the severity of skin and extracutaneous disease is a reflection of the type of mutation which is present, as well as the ultrastructural location of the targeted protein. Localized EBS, EBS-DM, and EBS generalized other (EBS-Koebner) result from dominant negative mutations within either the keratin 5 or keratin 14 gene. The site of mutation -- i.e., the location within the individual keratin filament -- is strongly correlated with EBS subtype, with EBS-DM patients having mutations within particularly structurally sensitive portions of the molecule. EBS with mottled pigmentation results from mutations within the keratin 5 gene, and EBS with muscular dystrophy is caused by mutations within the gene for plectin. A rare autosomal recessive form of EBS is known to result from mutations in the keratin 14 gene. EBS with pyloric atresia is caused by mutations either within the gene for plectin or the genes for the heterodimeric transmembrane protein, α6β4 integrin. Two suprabasal subtypes of EBS -- plakophilin deficiency [62] and lethal acantholytic EB [63] -- are known to arise as the result of mutations in the genes for plakophilin-1 and desmoplakin, respectively. The molecular etiology of EBS superficialis (EBSS) is still unclear although one family previously diagnosed with this was later shown to have a type VII collagen mutation similar to those seen in DDEB [64]. In support of EBSS being a distinctive entity, however, is the lack of any detectable type VII collagen mutation in the original published proband (unpublished data, 2009).

All types of DEB result from mutations within the type VII collagen gene (COL7A1) [68]. Of note, those with DDEB tend to have missense mutations resulting in glycine substitutions within the triple helical domain of type VII collagen. Analogous to what is seen in JEB-H and JEB-nH, patients with severe generalized RDEB may be either homozygous for their COL7A1 mutation or have two different mutations (i.e., "compound heterozygosity"), resulting in premature termination codons. In contrast, less severe types of mutations within the type VII collagen gene occur in patients with RDEB generalized other. In contrast to JEB, there are no mutational hotspots within the COL7A1 gene, so nearly every DEB family has its own unique site and/or type of mutation. A detailed summary of these mutations has been recently published [3].
Kindler syndrome, a rare autosomal recessive genodermatosis, is caused by mutations in the gene for kindlin-1, a recently discovered component of focal contacts in basal keratinocytes [69].

**Diagnosis/diagnostic criteria/diagnostic methods**

**Diagnosis criteria**

Each major EB type is diagnosed by determination of the ultrastructural level within which blisters develop following minor traction to the skin (Table 2). Subtypes are then defined on the basis of mode of transmission, immunohistochemical and electron microscopic findings, and clinical phenotype. Detailed summaries of the phenotypic features of each EB subtype have been recently published in an international consensus report on diagnosis and classification [3].

**Diagnostic methods**

**Postnatal diagnosis**

In the absence of a well characterized proband within the same kindred, every patient suspected of having inherited EB should have one or more skin specimens harvested and properly processed for diagnostic immunofluorescence antigenic mapping (IAM) and transmission electron microscopy (TEM) [22]. The precise ultrastructural level of mechanical fragility and inducible blister formation can be ascertained by one or both of these diagnostic techniques. Details as to optimal harvesting of specimens and the transport solutions needed have been reviewed elsewhere [3,22]. In general, though, the best samples for IAM and TEM are small punch biopsies and shave biopsies, respectively, harvested from nonblistered skin which has been first subjected to mild rotary traction. The conventional inclusion of EB-relevant antibodies used in IAM cannot be employed on conventional formalin-preserved tissue samples, due to loss of antigenicity in the latter tissues. Alternatively, attempts at using these paraffin embedded tissue blocks for subsequent TEM evaluation are also invariably suboptimal, due to differences in the fixatives used for tissue preservation.

As discussed in the 2008 consensus report, DNA mutational analysis for subclassification of EB is still primarily reserved for prenatal diagnosis (and even then only when the causative mutation has already been identified in a proband within the same family), or when preimplantation therapy is being considered, given the considerable problems that have been seen with genotype-phenotype correlation within most of the EB subtypes [3]. In addition, DNA testing is not routinely performed in the absence of prior tissue confirmation of the major type of EB which is present, since there are too many genes potentially involved in EB to make simultaneous screening of multiple genes either practical or affordable. If and when gene replacement therapy becomes a reality, then DNA mutational analysis will become part of the workup of all patients. Until that time, there may be other reasons to pursue DNA mutational analysis in selected cases. These include determination of the mode of transmission in patients suspected of having spontaneous mutations for DDEB (since the majority of these have been shown to have RDEB instead) or in patients involved in specific research projects which might benefit from full genotypic determination. Some families having one or more severely affected family members with autosomal recessive disease may also desire to screen clinically unaffected siblings for possible silent mutations, as well as their genetically unrelated spouses, prior to their pursuing pregnancy. Given how low the prevalence of autosomal recessive types of EB is within the general population, however, the likelihood of affected offspring arising from such pregnancies is extraordinarily low, making this very cost-ineffective.
Prenatal diagnosis
Through the early 1990s, prenatal diagnosis was routinely performed via either IAM or TEM on fetal skin specimens that were harvested, via ultrasound-directed fetoscopic sampling techniques, on or after about the 17th gestational week [73,74]. Since the mid-1990s, DNA mutational analysis has become the standard of care, using specimens obtained from chorionic villi, with the caveats noted above.

Differential diagnosis
The size and validity of the differential diagnosis generated on a child or adult with blistering of the skin is truly a reflection of the level of training and expertise of the physician. Indeed, in most situations the diagnosis of inherited EB should be obvious to a dermatologist; in only a minority of cases will there be any need for a more extensive differential diagnosis to be entertained prior to tissue confirmation. In the neonatal period, however, in utero herpes simplex infection might need be considered, especially if there is no family history of a blistering disease or if the clinical findings are very atypical for EB. Other conditions that may be considered as part of the differential diagnosis of EB are summarized in Table 6[3].

Genetic counseling [75]
Genetic counseling is best performed either by a medical geneticist or a dermatologist who has considerable experience with EB. Ultimately the diagnosis will be based on clinical phenotype, mode of transmission, IAM, TEM, and, when available, the mutational analysis of the affected proband. In-depth recommendations on the counseling of EB patients and their families have been recently published [75].

Management
The basic underlying tenets of care for all EB patients are avoidance of blistering (by meticulous protective padding of the skin) and prevention of secondary infection (by careful wound care, facilitated by the use of sterile synthetic non-adhesive hydrocolloid dressings). Patients with EB subtypes known to be at highest risk for specific extracutaneous complications need careful surveillance [76] for their occurrence, and implementation of appropriate interventions (medical; surgical; dental; nutritional; psychological; other) prior to the affected tissues becoming severely injured [24,25,76]. For example, early signs and symptoms of corneal disease activity need prompt evaluation by an ophthalmologist so as to prevent the development of permanent corneal scarring and impaired vision. Symptomatic esophageal strictures need to be dilated, oftentimes repeatedly, in order to maintain adequate intake of nutrients by mouth. Those children unable to take in sufficient nutrients by mouth are instead given nutrient supplements via gastrostomy [77]. Hand deformities, if they cannot be prevented by meticulous nightly wrapping of the digits, may be temporarily improved by surgical degloving procedures. Squamous cell carcinomas, which may arise as early as the second decade of life in patients with severe generalized RDEB and JEB-H, are treated by conventional wide excision, with careful follow-up to monitor for local or regional recurrence. Patients with generalized forms of JEB and RDEB need to be monitored by serial DEXA scans for possible osteoporosis or osteopenia, and in selected EB subsets other laboratory parameters (hematological; renal) or diagnostic tests (echocardiogram) should also be serially monitored or performed.

Several experimental approaches are now being explored for possible therapeutic use. These include, for autosomal recessive types of EB, ex vivo gene replacement [78,79], transplantation of allogeneic fibroblasts (in RDEB, to provide a source of normal type VII collagen) [80,81], transplantation of bone marrow-derived stem cells [82], and infusion of recombinant protein (i.e., type VII collagen for RDEB) [83]. For autosomal dominantly transmitted EB, a variety of studies are being pursued which are focused on means that possibly might either downregulate the dominant negative gene or, alternatively, compensate for its presence by the upregulation of other genes whose products might at least partially provide enhanced structural stability to the skin, thereby overriding the effect of the underlying mutation. Other clinical trials are now underway to look at possible means of enhancing wound healing, to include an ongoing one assessing the potential efficacy of the topical application of a small molecular weight protein, thymosin β4, to open wounds [84].

Prognosis
The prognosis of EB is highly dependent on the subtype of disease that is present. Most EB patients, particularly those with EBS and DDEB, have normal life expectancies, but significant morbidity may complicate some. In contrast, patients with JEB, most notably those with JEB-H, are at major risk of death during the first few years of life, and patients with RDEB, particularly those with severe generalized RDEB, are at risk of death on or after young adulthood from metastatic squamous cell carcinoma.

Unresolved questions
With rare exceptions, the underlying molecular cause of nearly every EB subtype has now been elucidated. Using such data, both postnatal and prenatal diagnoses are now possible for most clinical situations. It is clear, however, that some patients with identical mutations may have vastly different clinical phenotypes from others, suggesting the likely presence of other fac-
tors that might contribute to such differences. Work is now underway in several laboratories to search for possible modifier genes which might contribute to the overall clinical severity within some of these EB subtypes and might better explain the range of clinical phenotypes which is observed within individual EB subtypes.

The remarkably high frequency with which squamous cell carcinomas arise in RDEB, as well as the risk of metastasis and death following wide surgical excision of the primary tumors, is essentially unique. Inexplicably these tumors act in a very biologically aggressive way despite being usually very well differentiated histologically. Several leading EB research groups, therefore, are now focusing their efforts on trying to determine why RDEB-associated squamous cell carcinomas differ so drastically in their behavior from those seen in the normal adult population, with the hope that a better understanding of the biology of these tumors in RDEB may result in more successful treatments or more effective means of prevention.

It is still unknown whether gene replacement will ultimately become a realistic therapeutic modality, although in vitro cell and in vivo animal studies continue to look promising. It is also as yet unknown whether stem cell transplantation, or implantation of viable allogeneic fibroblasts into the skin of patients with RDEB, might

| Inherited or congenital disorders |
|----------------------------------|
| Epidermolysis hyperkeratosis (bullous congenital ichthyosiform erythroderma) |
| Ichthyosis bullosa of Siemens |
| Peeling skin syndrome |
| Pachyonychia congenita |
| Congenital porphyrias |
| Acrodermatitis enteropathica |
| Incontinentia pigmentii |
| Ectodermal dysplasia (ED) |
| AEC syndrome (Hay-Wells syndrome) |
| Congenital absence of skin (cutis aplasia) |
| Congenital erosive dermatosis with reticulate supple scarring |

| Acquired disorders |
|--------------------|
| Immunobullous disorders |
| EB acquisita |
| Linear IgA dermatosis |
| Bullous pemphigoid |
| Cicatricial pemphigoid |
| Neonatal herpes gestationis |
| Pemphigus |
| Infectious diseases |
| Herpes simplex |
| Staphylococcal scalded skin syndrome |
| Bullous impetigo |
| Other diseases or conditions |
| Bullous mastocytosis |
| Traumatic blisters (sucking; other) |

* modified from Fine JD et al, 2000 [5]
provide significant longterm clinical benefit and also be safely administered.

Abbreviations

Epidermolysis bullosa: EB; EB simplex: EBS; EB, Dowling-Meara: EBS-DM, EBS; Koebner: EBS-K; EB, mottled pigmentation: EBS-MP; EBS superficialis: EBS-S; Junctional EB: JEB; JEB, Epidermolysis bullosa dystrophica dermolytic: JEB-DND; Recessive dystrophic EB: RDEB; Severe generalized: RDEB Sev gen; RDEB, generalized other: RDEB gen other; RDEB, inversa: RDEB-I; National EB Registry (USA): NEBR; Transmission electron microscopy: TEM, Immunofluorescence antigenic mapping: IAM.

Competing interests

The author declares that he has no competing interests.

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