PURPOSE: To determine the frequency of ocular manifestations in inherited epidermolysis bullosa (EB) within the continental United States and to define the estimated cumulative risks of developing nonscarring (blisters or erosions) and scarring corneal manifestations within each major EB subtype over time.

DESIGN: Observational (cross-sectional and longitudinal).

METHODS: Up to 16 years of longitudinal follow-up was conducted on 3,280 consecutively enrolled patients in the National EB Registry, an epidemiologic study funded by the National Institutes of Health. Data were stratified by major EB type and subtype. Frequencies of occurrence were determined for eight variables (corneal erosions or blistering; corneal scarring; symblepharons; blepharitis; ectropions; lacrimal duct obstruction; impaired vision; blindness) by contingency tables, and cumulative risks were generated by life table analysis technique.

RESULTS: The most common ocular manifestations were corneal erosions and blisters. Frequencies mirrored relative severity of skin disease, with 74.10% of all patients with recessive dystrophic EB, Hallopeau-Siemens (RDEB-HS) and 47.50% of all patients with junctional EB, Herlitz (JEB-H) experiencing at least one episode. Lower frequencies were noted for corneal scarring. Symblepharons and ectropions were most commonly seen in inversa RDEB and JEB-H, respectively. Blindness was reported in 6.47% of RDEB-HS patients. The cumulative risks of nonscarring and scarring corneal lesions in JEB-H at age 5 are 83.18% and 27.08% and at age 25 are 83.18% and 72.22%. With time, the cumulative risk of each in RDEB-HS approached that reported in JEB-H patients.

CONCLUSION: Ocular disease activity, particularly corneal, is common in some EB subtypes. Careful ophthalmologic examination should become an integral part of the management of all patients with inherited EB. (Am J Ophthalmol 2004;138:254–262. © 2004 by Elsevier Inc. All rights reserved.)

INHERITED EPIDERMOLYSIS BULLOSA (EB) IS ONE OF THE most devastating chronic diseases known to mankind. It encompasses four major groups of skin diseases—EB simplex (EBS), junctional EB (JEB), dominant dystrophic EB (DDEB), and recessive dystrophic EB (RDEB)—each of which is characterized by the presence of marked mechanical fragility of epithelial tissues and the repeated development of blisters and open, nonhealing wounds. Each of these major EB types is defined by distinct differences in the ultrastructural level within which blisters develop in affected tissues (Table 1).

At least 23 phenotypes of inherited EB have been described to date. Each reflects differences not only in the variety and severity of clinical manifestations but also in the gene(s) that are targeted for mutation. Mutations arising in at least 10 genes have now been shown to result in at least one subtype of inherited EB (Table 2); these have been reviewed in detail elsewhere. Each of the three chains of laminin-5, and type VII collagen. The presence of such mutations results in the synthesis (and usually rapid
degradation) of mechanically unstable proteins that otherwise normally function as cytoskeletal or matrix-associated structural elements or adhesion molecules. As such, affected tissues are exceedingly fragile and tear or blister after even the most minor of trauma or traction to their surfaces.

The first report of eye involvement in inherited EB was published in 1904. Since then, limited numbers of case reports and a few case series have confirmed that various types of pathology may arise within the external eye in the setting of at least some subtypes of inherited EB and in its autoimmune counterpart, EB acquisita. These published data, however, do not represent longitudinal data collection, nor have they been derived from studies designed to permit generalization to an entire population or to allow statistical estimation of the cumulative risk for the development of any of the most severe ocular sequelae.

In 1986 the National Institutes of Health (NIH) established the National EB Registry, an epidemiologic project having both cross-sectional and longitudinal components. One of its major goals was to determine the risk of selected extracutaneous outcomes in inherited EB. During its 16 years of continuous funding, 3,280 patients were enrolled and evaluated throughout the continental United States. The demographics of this study population were shown to closely mirror that of the American population, allowing generalization across the United States. The distribution of patients by major EB type and subtype was also shown to closely mimic that seen within much smaller cohorts of EB patients elsewhere in the world, suggesting that these data are applicable to EB patients everywhere.

On the basis of rigorous analysis of this registry’s database, we can now more precisely measure the impact of

### TABLE 1. Ultrastructural Levels of Blister Formation in Inherited Epidermolysis Bullosa (EB)

<table>
<thead>
<tr>
<th>Major EB type</th>
<th>Level of tissue cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB simplex</td>
<td>Intraepidermal (usually within the lowermost portion of the basal keratinocyte just above the level of the plasma membrane)</td>
</tr>
<tr>
<td>Junctional EB</td>
<td>Within the lamina lucida of the basement membrane zone comprising the dermal-epidermal junction</td>
</tr>
<tr>
<td>Dystrophic EB (both autosomal dominant and autosomal recessive types)</td>
<td>Just beneath the lamina densa of the dermal-epidermal junction</td>
</tr>
</tbody>
</table>

### TABLE 2. Inherited Epidermolysis Bullosa (EB): Targeted Proteins for Mutations and Their Associated Ultrastructures

<table>
<thead>
<tr>
<th>Major EB Subtype</th>
<th>Targeted Protein</th>
<th>Associated Ultrastructure or Location of the Mutated Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB simplex (all major subtypes except EB simplex with muscular dystrophy and EB simplex Ogna)</td>
<td>Keratin 5 or 14</td>
<td>Keratin intermediate filaments (within basal keratinocytes)</td>
</tr>
<tr>
<td>EB simplex with muscular dystrophy</td>
<td>Plectin</td>
<td>Innermost portion of the hemidesmosome</td>
</tr>
<tr>
<td>EB simplex, Ogna</td>
<td>Plectin</td>
<td>Innermost portion of the hemidesmosome</td>
</tr>
<tr>
<td>Junctional EB, Herlitz</td>
<td>Laminin-5</td>
<td>Anchoring filaments (present within the lamina lucida) and hemidesmosome</td>
</tr>
<tr>
<td>Junctional EB, generalized non-Herlitz subtypes</td>
<td>Laminin-5; type XVII collagen</td>
<td>Anchoring filaments (present within the lamina lucida) and hemidesmosome</td>
</tr>
<tr>
<td>Junctional EB-pyloric atresia syndrome</td>
<td>α6β4 integrin</td>
<td>Hemidesmosome and uppermost lamina lucida</td>
</tr>
<tr>
<td>Dominant dystrophic EB</td>
<td>Type VII collagen</td>
<td>Anchoring fibrils (present just beneath the lamina densa)</td>
</tr>
<tr>
<td>Recessive dystrophic EB</td>
<td>Type VII collagen</td>
<td>Anchoring fibrils (present just beneath the lamina densa)</td>
</tr>
</tbody>
</table>
ocular disease, to include accurate estimation of the cumulative lifetime risk of corneal blistering, erosion, and scarring, for each of the major types and subtypes of inherited EB.

DESIGN

THIS WAS AN OBSERVATIONAL, CROSS-SECTIONAL, LONGITUDINAL STUDY.

METHODS

● SETTING: This was a multicenter, institutional study.

● STUDY POPULATION: Data were obtained from 3,280 consecutively enrolled EB patients who were seen on behalf of the National EB Registry from September 1986 through April 2002, when formal federal funding for this NIH-supported project ended. During these 16 years of continuous NIH funding, work was carried out by a number of coinvestigators at several institutions (see Appendix). The authorship of the present study represents the research team at the project’s Data Coordinating Center that took ultimate responsibility for data validation and the performance and interpretation of all biostatistical analyses, in addition to playing a pivotal role in data collection from the majority of the project’s patients.

● OBSERVATION PROCEDURES AND INSTITUTIONAL REVIEW BOARD APPROVAL: A comprehensive data instrument containing nearly 1,000 possible data entries was employed. The instrument comprised a detailed questionnaire, which included patient demographics, past and present medical histories, family history, and socioeconomic parameters, as well as the findings from physical examination and diagnostic laboratory studies. This instrument was created, with the assistance of the NIH, by a committee composed of the original four principal investigators of the Registry and selected colleagues who worked at the same regionally distributed universities (Rockefeller University, Washington University, University of Alabama at Birmingham, and University of Washington), where work on this project first took place. The instrument was then modified for approval for such use by the institutional review boards at each of the participating institutions. Final modifications were made as the result of recommendations from the Office of the Management of the Budget. During the last 5 years of funding, all work was confined to the University of North Carolina at Chapel Hill and Stanford University and was conducted under the auspices of the NIH-supported General Clinical Research Centers at each of these universities.

Whenever possible, each enrollee was seen and physically examined at least once by one of the project’s principal investigators. Data collection was then entered into specially designed templates originally based on Clinfo and later on EpiInfo software (Centers for Disease Control, Atlanta, Georgia). SAS data sets (SAS Institute, Cary, North Carolina) were subsequently generated to facilitate the performance of more sophisticated biostatistical analyses.

In each case, the diagnosis of EB was confirmed by immunofluorescence antigenic mapping, EB-specific monoclonal antibody studies, and transmission electron microscopy. Most of these studies were performed within designated core laboratories of the National EB Registry. Photomicrographs were evaluated by the Registry staff whenever diagnostic studies were done elsewhere, to validate and standardize each diagnosis. Each patient was further subclassified as to EB subtype by a widely used classification scheme that was reported in 1991 and updated in 2000 by an international panel of EB experts.

For the purpose of the analyses reported within this study, we have separated our patient population into several mutually exclusive EB subtypes, following the detailed criteria of the most recent classification scheme: EBS, Weber-Cockayne (EBS-WC); EBS herpetiformis, Dowling-Meara (EBS-DM); EBS, Koebner (EBS-K); EBS, all others (EBS-O); junctional EB, Herlitz (JEB-H); junctional EB, non-Herlitz (JEB-nH); dominant dystrophic EB (DDEB); generalized recessive dystrophic EB, Hallopeau-Siemens (RDEB-HS); recessive dystrophic EB, inversa (RDEB-I); generalized recessive dystrophic EB, non-Hallopeau-Siemens (RDEB-nHS). Data were sufficient on 2,748 patients (83.8%) enrolled within the NEBR project to permit subclassification into these 10 major EB subtypes. This served as the final subpopulation from which ocular disease data were extracted. Because occasional patients were unable to provide information on each ocular manifestation being sought, the N value listed in Table 3 represents the average number of respondents for each specific ocular finding.

Approximately 450 well-classified subjects were further randomly selected for longitudinal follow-up every 2 years during the last 10 years of this project. This nested subpopulation was chosen so as to maximally sample those EB subtypes most at risk for significant extracutaneous or severe cutaneous disease activity and for the development of clinically relevant sequelae.

All biostatistical analyses were conducted under the direct supervision of the project’s designated biostatistician (C.S.), who remained masked as to the identity of each subject.

Results pertinent to this study were initially generated as simple frequencies by mean of contingency tables. Each result was stratified by major EB subtype.

Cumulative probabilities for corneal blisters or erosions, as well as corneal scarring, were then calculated for each major EB subtype, by conventional life table analysis (Kaplan-Meier) technique using SAS software.
technique is the most widely used biostatistical method for estimating survival (i.e., the lack of development of a measured outcome, in this case corneal disease activity) among a collected group of subjects who had been followed over time. It requires data on each subject as to not only the development of a particular outcome of interest but also the time at which this occurs. This technique then allows one to estimate the cumulative probability or risk that a particular outcome or event will or will not have occurred by any given period of time within the entire study population. In the case of our own particular data, we chose to measure the risk of an event occurring ("failure") rather than not occurring ("survival"). As such, if all patients were predicted to have developed a particular ocular complication by time X, then the cumulative risk at that point in time would be 100% (or the cumulative probability would be 1.0). Such a technique also permits the determination of the probability (or risk) of the event occurring within isolated windows of time (i.e., conditional probabilities) rather than over lifetime (i.e., cumulative probability). For the purpose of this study, we have chosen to present cumulative risk data, because our interest has been to document the magnitude of major ocular complications over the lifetime of patients representative of specific EB subtypes.

Computer-generated graphs were created using Excel (Microsoft, Seattle, Washington, USA).

**MAIN OUTCOME MEASURES:** Frequencies of occurrence were determined for eight ocular manifestations (corneal erosions or blisters; corneal scarring; symblepharons; blepharitis; ectropions; lacrimal duct obstruction; impaired vision; blindness).

Cumulative risks were estimated for the occurrence of blisters or erosions and for scarring of the cornea at yearly intervals until age 10 and in 5-year intervals thereafter.

**RESULTS**

THE MOST COMMON OCULAR FINDING IN OUR STUDY POPULATION was corneal blister formation, manifested as either intact vesicles or corneal erosions (Table 3). This most often occurred in patients having the two most severe types of EB, junctional EB and recessive dystrophic EB. Within our JEB subpopulation, this was more commonly seen in the more severe JEB subset, Herlitz disease, with nearly half of all patients having experienced this abnormality. In contrast, only about one quarter of all non-Herlitz JEB patients had a history of corneal blistering. Similarly, nearly three quarters, one third, and one third of all patients with RDEB-HS, RDEB-nHS, and RDEB-I, respectively, had experienced at least one episode of corneal blisters or erosions. Among all other EB subtypes, the frequency of corneal blister formation was low, ranging from 0.92% (in the mildest EB subtype, Weber-Cockayne EBS) to 6.19% (in the most severe EBS subtype, Dowling-Meara disease).

The frequencies of corneal scarring were lower than that of blisters and erosions across all major EB types and subtypes. This makes intuitive sense, because scarring would not be expected to occur in every patient, especially if blistering had occurred only once or infrequently or if it was self-limited in its duration. The highest frequencies were seen in RDEB-HS (50%), RDEB-I (29.4%), and JEB-H (26.8%).
Blepharitis was an uncommon finding in EB, with highest frequencies observed in RDEB-HS and RDEB-I (about 18% in each) and in both subtypes of JEB (6% to 7%).

Symblepharon formation was confined to JEB and RDEB patients. The highest frequencies were seen in RDEB-HS (10%), RDEB-I (12%), and JEB-H (5%). This would be consistent with the severity of other external eye involvement noted in these three major EB types.

Ectropion formation was most often noted in JEB-H (Figure 1), occurring in approximately 14% of all cases. This retraction, scarring, and eversion of the lower eyelids is compatible with the presence of chronic exuberant granulation tissue in adjacent skin. About half as many patients with RDEB-HS were reported to have had some evidence of ectropion formation. In our experience, those ectropions were much milder than those seen in patients with JEB-H.

Lacrimal duct obstruction was reported rarely in each major EB subtype. Higher levels were noted only in RDEB, especially in those patients with inversa disease (nearly 12%). The fact that RDEB-I patients have the highest frequency of this finding may be compatible with this EB subtype’s marked prevalence for epithelial blistering within other mucosal tissues to include the oral cavity, esophagus, urethra, and introitus.

In an effort to be comprehensive, our data collection instrument also included questions about impaired vision and blindness. Complaints of impaired vision (cause undefined) appeared to be increased only in RDEB and only in the Hallopeau-Siemens and inversa subtypes. The frequency of this complaint was approximately 40% in both subtypes. The only apparent increased frequency in blindness was within our RDEB-HS subtype (6%). Review of these patients’ medical and hospital records provided details in only three patients. In two, blindness was attributed to severe corneal scarring. In a third, retinal separation, presumably unrelated to EB, was reported.

Using the life table analysis technique, we estimated the cumulative risk of corneal blistering or erosions for each major EB subtype (Figure 2). By age 1, the cumulative risk of these lesions was already 27.12%, 18.64%, 10.43%, and 8.79% in JEB-H, RDEB-HS, RDEB-nHS, and JEB-nH, respectively. This risk reached a plateau of 83.18% in JEB-H by age 5. In RDEB-HS, essentially the same end point (79.35%) was reached by age 35, although 63.53% and 71.15% of all patients were predicted to have experienced corneal blisters or erosions by ages 10 and 20, respectively. The cumulative risk of corneal blistering or erosions in JEB-nH reached 46.5% by age 40, roughly half of that seen in JEB-H patients. Similarly, the maximum cumulative risk in RDEB-nHS achieved a level approximately half (35.11%) of the maximum level in RDEB-HS by age 30. An almost identical curve was observed for RDEB-I. Among EBS patients, only those with generalized Dowling-Meara disease were at significant risk for this outcome, with a cumulative risk of 7.73% predicted by age 20.

Life tables were also generated for corneal scarring (Figure 3). The trends were similar to those seen with corneal blistering or erosions, although the absolute values were lower. Corneal scarring was predicted to occur in 3.45%, 5.93%, and 3.51% of all patients with JEB-H, RDEB-HS, and RDEB-I, respectively, by age 1. The highest cumulative risk (72.22%) was seen in JEB-H and was achieved by age 20. In comparison, the cumulative risks by age 20 in RDEB-HS, RDEB-nHS, and RDEB-I were 51.23%, 16.82%, and 21.21%, respectively. The maximum cumulative risk (or plateau value) was 60.34% by age 35 in RDEB-HS, 23.55% by age 50 in RDEB-nHS, 29.97% by age 35 in RDEB-I, and 5.18% by age 40 in EBS-DM.

Figure 4 graphically summarizes these findings by comparing the cumulative risks for scarring vs nonscarring corneal disease activity in the two clinically most severe EB subtypes, RDEB-HS and JEB-H.

**DISCUSSION**

A VARIETY OF OCULAR FINDINGS HAVE BEEN REPORTED IN inherited EB. This is not surprising, given the many biochemical and ultrastructural similarities shared between skin and cornea, particularly at the level of the plasma membrane and the epithelial-dermal basement membrane zone.

Ocular abnormalities may be acute or chronic, symptomatic or asymptomatic, and of variable clinical severity.
Ocular disease activity has been reported as early as 1 month of life. 29

The most common ocular findings in EB include red watering eyes, 34 photophobia, 33, 45 ocular pain, 31, 33, 45 conjunctival injection, 25 conjunctival edema, 34 blepharoconjunctivitis, 33, 36, 38 exposure keratitis, 26, 28, 37 corneal erosions or abrasions, 24, 28, 31, 33, 35–38 corneal ulcerations, 45 corneal bullae, 34 corneal opacities, 34, 36 corneal scarring, 28, 34–37 limbal broadening, 34, 36, 38 pannus formation, 34, 35, 37 symblepharons, 25, 27, 38 and ectropions. 35 Lacrimal duct obstruction has been reported. 35 Reduced tear break-up time was also noted in one 8-year-old boy with JEB-H, 28 as was shrinking of the conjunctiva in two other patients. 21, 22 Eyelashes may be sparse in some patients. 28, 34 Ankyloblepharons may also rarely occur. 35 Blisters on the adjacent epithelial surfaces of the eyelids are not uncommon. These collective ocular findings are most commonly seen in junctional and recessive dystrophic forms of EB but have also been reported in the Koebner and Dowling-Meara subtypes of generalized EB simplex.

Very few large series of EB patients have been studied. One of the largest, involving 181 consecutive patients who were seen and given full ophthalmologic examination at London’s Great Ormond Street Children’s Hospital from 1980 to 1996, was reported by Tong and associates. 37 The overall frequency of ocular complications was 12%, 40%, 4%, and 51% in their children with EBS, JEB, DDEB, and RDEB, respectively. The only finding seen in a single patient with DDEB was conjunctival blistering. The only findings in EBS were present in those having the usually clinically severe Dowling-Meara subtype. Of these, 12% had peripheral corneal vascularization; eyelid blistering and corneal abrasions were also noted. In contrast, 14% of RDEB patients had a history of recurrent ocular erosions, 68% had some type of corneal complication (abrasions; scarring; pannus formation), 8% had exposure keratitis.
with ectropions of both upper and lower lids, 24% had conjunctival involvement, and 14% had eyelid blisters. The most common findings in their JEB patients were corneal scarring (20%) and exposure keratopathy (33%). Miscellaneous ocular findings in rare patients included amblyopia, squints, lacrimal punctal occlusion, punctal papilloma of the eyelid, subconjunctival hemorrhage, pseudopterygia, microophthalmos, and anterior polar cataract with astigmatism. Lin and associates reported findings in 204 patients with EB seen at Rockefeller University (New York, New York) from 1986 to 1993. Findings were similar in type and frequency to those reported by Tong and associates.

Gans reported the findings in 78 EB patients studied in nonlongitudinal fashion at Washington University (St Louis, Missouri) from 1979 to 1986. The most common finding was the presence of corneal erosions in 55.5% of patients with JEB-H and 52.9% of patients with RDEB. About one quarter of the RDEB patients had evidence of corneal scarring; blepharitis and eyelid blistering each occurred in about one fifth.

In the current study, we have presented data that were systematically obtained from a study population of 3,280 consecutively enrolled patients in the National EB Registry. This study represents the largest cohort of EB patients ever assembled in the world and reflects up to 16 years of methodical clinical follow-up. Although the primary design of the study was a cross-sectional one, the majority of patients had some longitudinal data collection as well. About one eighth of the entire study population was also randomly selected for formal prospective evaluation every 2 years. As discussed previously and as depicted in Table 3, some EB subtypes (particularly JEB-H and the three major subtypes of RDEB) are at a much higher risk for developing selected external eye complications. We have further demonstrated by the life table analysis technique that these four clinically severe EB subtypes are at the highest cumulative risks for the development of corneal blisters, erosions, and scarring. As a correlate, we have quantified the cumulative risks of these complications over time and have confirmed that corneal disease activity may occur even within the first year of life.

Collectively, these data demonstrate the magnitude of external eye disease activity within each major EB subtype. The relative differences that we have documented in the frequencies and cumulative risks for ocular complications may be used clinically to develop more effective surveillance strategies for the prospective evaluation and care of children and adults with inherited EB. Given the magnitude and clinical impact of external eye involvement in this disease, it is clear that ophthalmologic evaluation should be considered an essential component of the overall management of patients with inherited EB.

ACKNOWLEDGMENTS

The senior author (J.D.F.) gratefully acknowledges federal grant support for the National Epidermolysis Bullosa Bullosa Registry throughout its 16-year existence. Availability of the many resources of a National Institutes of Health–supported General Clinical Research Center at the University of North Carolina at Chapel Hill was also critical to the success of this project during its last 12 years. We gratefully acknowledge the contributions of several other physicians to patient recruitment and data collection on behalf of the Registry throughout at least portions of its existence, most notably Drs Joseph McGuire and Eugene Bauer (Stanford University), D. Martin Carter (Rockefeller University), and Virginia P. Sybert (University of Washington). Finally, we wish to thank each of the nearly 3,300 enrollees.
in the National EB Registry, many of whom had to travel hundreds of miles for evaluation and follow-up by the Registry, for their enthusiasm in enrollment and for their continued interest in, encouragement of, and cooperation in participating in such a lengthy, time-consuming, and physically difficult study. Without such personal commitments on their part, such work would not have been possible.

REFERENCES


APPENDIX

NATIONAL EPIDERMOLYSIS BULLOSA REGISTRY COLLABORATING INSTITUTIONS

Data Coordinating Centers: Rockefeller University, 1986 to 1992; University of North Carolina at Chapel Hill, 1992 to 2002

Clinical Centers or Subcontract Sites for Regional Data Collection: Rockefeller University (1986 to 1997); University of North Carolina at Chapel Hill (1990 to 2002); Stanford University (1989 to 2002); Washington University (1986 to 1989); University of Alabama at Birmingham (1986 to 1990); University of Washington (1986 to 1997); Children’s Memorial Hospital, Chicago (1992 to 1995); University of Colorado (1992 to 1997)