EB Simplex (EBS)

Intermediate EBS (previously known as EBS generalized-severe, EBS Koebner)
Severe EBS (previously known as EBS generalized-severe, EBS Dowling Meara
EBS, intermediate with Muscular Dystrophy
EBS, severe with Pyloric Atresia
Other EB Simplex Subtypes

EB simplex (EBS) is the most common type of EB. It also is known as intraepidermal or epidermolytic EB. According to National EB Registry data, more than half of people with epidermolysis bullosa have EB simplex. EBS can be further classified based on the clinical presentation, with variations such as Localized EBS, Intermediate EBS, Severe EBS, EBS intermediate with muscular dystrophy and EBS severe with pyloric atresia.

EB simplex usually is caused by a mutation in the gene for keratin 5 or keratin 14. These genes encode keratin proteins, which form one of the major structural components of the superficial layer of the skin, the intermediate filaments. The presence of abnormal keratins results in weakness or fragility of the epidermis. With trauma and friction, the epidermis easily shears, and superficial blisters form. As these blisters are relatively superficial, they burst or rupture easily, leaving behind shallow erosions.

Rarely, people with EBS may have a mutation in another gene, either plectin (associated with EBS intermediate with muscular dystrophy, EBS severe with pyloric atresia and EBS Ogna), a6b4 integrin (associated with EBS severe with pyloric atresia), plakophilin-1 (associated with plakophilin deficiency) or desmoplakin (associated with lethal acantholytic EB).

Typically, EBS blisters heal without the development of a scar. When scars are seen in the setting of EB simplex, they generally are the result of infection. Post-inflammatory hypopigmentation (lighter areas of skin) or hyperpigmentation (darker areas of skin) occurs commonly with EBS. As blisters heal, the newly formed skin appears lighter or darker than unaffected skin. This change in skin color usually is temporary, although it may take months before the skin color returns to normal.

EB simplex usually is inherited as a dominant condition. In such cases, only one parent has EBS. The affected parent has one abnormal copy of the involved keratin gene and one normal copy of the keratin gene (humans have two copies of most genes). With each pregnancy, there is a 50-50 chance that the abnormal gene will be passed along, resulting in a child with EB simplex. Likewise, there is a 50 percent chance that the normal gene will be passed to the child, resulting in a child who does not have EB. (Figure 2) Rarely, a child affected with EBS may not have an affected parent; this is known as a de novo mutation, which means that the mutation occurred in the egg or the sperm before fertilization and is not carried by either parent. Very rarely, EBS may be transmitted in an autosomal recessive form, in which both parents are normal without any manifestations of EBS; however, they each carry an abnormal copy of the keratin gene. In this instance, there is a 25% chance that the child will inherit both abnormal keratin genes, in which case he or she will be affected.

Localized EBS

Blisters occur primarily on the palms and soles, although any part of the skin may blister in response to friction or trauma. It is not unusual to develop blisters on other parts of the body when there is increased friction on the skin, such as with horseback riding, which may cause blisters on the buttocks and thighs. Another common problem are blisters due to tight clothing or waistbands. Blisters occur more frequently when the weather is hot and humid. During summer, when the pavement is hot, many people report developing blisters on their feet after walking from a parking lot into a store or work.

Localized EBS usually presents during infancy or early childhood, when the baby is kicking in the crib or starting to crawl or walk. Sometimes, it does not appear until the individual is older; it even has been reported as appearing in adults who, after joining the military and being required to march long distances, developed blisters.

Thickening of the skin on the palms and soles (keratoderma) may occur in some adults with Localized EBS and, occasionally, fingernails and toenails become thickened and dystrophic (abnormal in appearance) with recurrent blistering. Blistering usually is confined to the skin, except during infancy, when oral blisters may develop due to sucking during feeding or when a pacifier is used. Milia and scarring do not usually occur, and there is no increased incidence of dental caries (cavities) or dental enamel problems. Affected children typically do not have poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

Intermediate EBS

Intermediate EBS is a generalized form of EBS, meaning that blisters occur anywhere on the surface of the skin in response to friction or trauma. Blisters are reported to occur more frequently during the summer months when the weather is hot and humid. Intermediate EBS usually presents at birth or during infancy. Milia and scarring are uncommon in this subtype. There may be mild involvement of the mucous membranes, and eye involvement may rarely occur. Thickening of the skin on the palms and soles (keratoderma) may occur, and fingernails and toenails may become thickened and dystrophic (abnormal in appearance) with recurrent blistering.

Affected children do not typically have poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes, or genitourinary tract. There is no increased risk of skin cancer.

Severe EBS

Severe EBS is another generalized form of EBS. It probably is the most severe form of EB simplex, but, as with all subtypes of EB, the severity is variable. Infants often are born with widespread blisters on the face, body and limbs.Congenital localized absence of skin (also known as aplasia cutis congenita and, historically, as Bart's syndrome) may be present at birth and usually affects the arms and/or legs. Often, with severely affected infants, parents report the occurrence of as many as 200 blisters per day. The widespread blistering of Severe EBS may lead to serious infection, along

with feeding problems and the development of failure to thrive. Death rarely has been reported during infancy.

Blisters occur more frequently the weather is hot and humid. Increased physical and emotional stress also have been reported to cause an increase in blistering. Interestingly, some individuals with Severe EBS have reported an improvement in blistering when they have a fever. Blisters tend to decrease in number and severity for most patients as they grow older. Some people with Severe EBS even report having "grown out of it" by the time they begin grade school.

Thickening of the entire skin on the palms and soles (keratoderma) commonly occurs due to recurrent blistering. If the keratoderma is severe enough, it may cause difficulty walking and eventually lead to contractures of the toes, in which case surgical intervention (contracture release) may be required. Blisters may occur beneath the keratoderma and are very painful and difficult to drain, exacerbating problems with pain and walking. Fingernails and toenails may become thickened and dystrophic (abnormal in appearance) with recurrent blistering. Nail loss may occur. Milia (tiny superficial white cysts in the skin) may develop after blisters have healed. Blisters commonly occur in the mouth.

Affected children typically do not have poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes, or genitourinary tract with the exception of chronic constipation and occasionally esophageal strictures. There is no increased risk of skin cancer.

EBS, Intermediate with Muscular Dystrophy

EBS, intermediate with Muscular Dystrophy is an extremely rare, recessively inherited form of EB simplex that results from mutations in the plectin gene. Absence of the plectin protein has been found to be responsible for the structural failure of the skin and muscles, resulting in EB simplex and muscular dystrophy. Although generalized blistering usually presents at birth, the onset of the muscular dystrophy usually does not occur until infancy or adulthood. Milia, scarring and nail dystrophy are common. Keratoderma of the palms and soles may occur but is rare. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Blistering of the mouth does not occur, and affected children typically do not develop poor growth and anemia.

With the exception of pyloric atresia and chronic constipation, affected children typically do not have problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

EBS, Severe with Pyloric Atresia

EBS, severewith Pyloric Atresia is another very rare form of EB simplex that is thought to be autosomal recessive in inheritance and is due to plectin mutations. It presents at birth with widespread blistering. Pyloric atresia is the presence of a stricture or narrowing in the stomach at the pylorus, a muscle, that prevents stomach contents from passing into the intestines. Affected infants develop abdominal distention, vomiting, dehydration and electrolyte abnormalities within the

first few weeks of life, and death may occur if pyloric atresia is not recognized and treated promptly through surgery.

Diagnosis may be aided by an ultrasound or contrast-enhanced X-ray such as an upper gastrointestinal barium study. Although milia do not occur, scarring is common. Congenital localized absence of skin has also been reported with EBS, severe-Pyloric Atresia. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Blistering of the mouth is common, and affected children typically develop poor growth and anemia. With the exception of pyloric atresia and chronic constipation, affected children typically do not have problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer. Other reported features include deformity of the ears and nose, joint contractures and failure of the testicles to descend (cryptorchidism).

Other EB Simplex Subtypes

Autosomal recessive EBS, intermediate or severe is a rare form of EB simplex due to mutations in keratin 14 or 5. It presents at birth with generalized blistering; blistering around the anus and genitalia may occur. Milia and scarring may be observed, and dystrophic nails are common. Keratoderma may be seen. Although dental enamel is normal, affected children appear to have a slightly increased tendency to dental caries. Blistering of the mouth is common. Affected children typically do not have poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract with the exception of chronic constipation. There is no increased risk of skin cancer.

EBS with mottled pigmentation is a rare autosomal dominant form of EB simplex caused by mutations in keratin 5. It presents at birth with widespread blistering. Milia and scarring typically do not occur, although a mild form of keratoderma may occur. Nail dystrophy usually is mild. The characteristic feature of the disease is the development of a brown skin discoloration after recurrent blistering on the body and extremities. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Blistering of the mouth does not occur, and affected children typically do not develop poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

EBS-migratory circinate is another rare autosomal dominant form of EB simplex caused by a mutation in the keratin 5 gene. Widespread blistering occurs at birth. The characteristic feature is the development of patches of erythema (redness) that appear to “migrate” on the skin, leaving behind hyperpigmentation or brown discoloration of the skin. Milia and scarring typically do not occur. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Blistering of the mouth does not occur, and affected children typically do not develop poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

EBS-Ogna is a rare autosomal dominant form of EB simplex caused by a mutation in the plectin gene. It is characterized by blistering at birth that predominantly involves the hands and feet, although more generalized blistering also may develop. Milia and scarring typically do not occur. The characteristic features of the disease is the development of very thickened nails, termed

onychogryphosis, as well as a tendency to bruise. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Blistering of the mouth does not occur, and affected children typically do not develop poor growth, anemia, or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

Lethal acantholytic EBS is an extremely rare form of autosomal recessive EB simplex that is caused by mutations in the desmoplakin gene. Only two affected newborns have been described, both of whom died soon after birth. In the affected newborns, generalized erosions and oozing at birth such that the skin appears to “peel off” without true blister formation was reported. Milia and scarring were not observed, although significant nail dystrophy was seen. Alopecia of the scalp (hair loss or poor growth) and the presence of teeth at birth (neonatal teeth) were reported. Blistering of the mouth and intestines/gastrointestinal tract, genitourinary tract and trachea/respiratory tract was noted. Eye involvement was not reported.

Plakophilin deficiency, also known as ectodermal dysplasia-skin fragility syndrome, is another very rare autosomal recessive form of EB simplex caused by plakophilin mutations. Generalized erosions with rare blisters are present at birth. Milia and scarring are not seen. Nail dystrophy is common, as is sparse hair. Keratoderma with fissuring of the palms and soles, fissuring of the tongue and characteristic fissuring around the mouth are characteristic. Dental enamel is normal, and there does not appear to be an increased tendency to dental caries. Poor growth, constipation, esophageal stricture, sparse eyelashes and inflammation of the eyelids (blepharitis) have been reported. Involvement of the trachea/respiratory tract and genitourinary tract have not been reported.

Junctional EB

Junctional EB (JEB), also called lamina lucidoytic EB, is caused by a mutation in one of these genes: **laminin-332 (also known as laminin-5), collagen XVII or α6β4 integrin.** These genes contribute to forming the structural components of the skin known as hemidesmosones and anchoring filaments, which keep the outer layer of the skin, the epidermis, attached to the deeper layer of the skin, the dermis. When these components are abnormally formed, the layers of the skin will separate, and a blister will form.

Junctional EB is the least common subtype of EB. According to theNational EB Registry data, approximately 10 percent of people with epidermolysis bullosa have junctional EB. All subtypes of junctional EB are inherited as a recessive disorder. Both parents of an affected child carry an abnormality or mutation in the affected gene. With recessive traits and disorders, two copies of the gene are required in order for the trait or disorder to be present; therefore the parents do not have EB. They are called “carriers.” In order for EB to occur in their children, both parents must pass the abnormal copy of the gene to the child. There is a 25 percent chance (1:4) with each pregnancy that the child will have the disorder; likewise, there is a 75% chance that the child will not, although the child still may be a carrier for the gene mutation.

Severe JEB

Severe JEB (previously know as JEB generalized severe, Herlitz JEB) is the most severe subtype of JEB. It is caused by mutations in the laminin-332 gene. Affected infants generally present at birth with severe, widespread erosions and blisters, although, in some cases, blistering at birth may be mild. After affected newborns are exposed to diapering, bathing and handling, the skin begins to blister and shear off, leaving large denuded areas. Erosions (sores) of the fingertips and slow or non-healing facial wounds are telltale indications of JEB, typically Severe JEB.

Commonly, blisters and slow or non-healing erosions are seen on these infants in the diaper area, around the nose and mouth, on the nail beds and the fingertips and toes, on the scalp and on the neck. Significant pain is reported by most parents and caregivers. Milia, scarring, alopecia and other scalp abnormalities and nail dystrophy are common. The development of excess granulation tissue is characteristic. Poor dental enamel, oral erosions and dental caries are common. Poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract are common. Laryngeal blisters and resultant scars cause a hoarse cry during infancy. Tracheal blistering and scarring may cause occlusion of the trachea and suffocation if not recognized and treated.

Painful blisters and erosions may develop on the conjunctiva of the eye. Ectropion is another feature of JEB eye involvement where the eyelids are turned outward or pulled away from the eyes such that it becomes impossible to close the eyes. This is seen most often with the lower lids but also may be seen in the upper lids. With JEB, this finding occurs as a result of scarring. Surgical repair rarely is successful. Ectropion leaves the eyes susceptible to drying and vulnerable to foreign objects and dust particles, leading to further irritation and blistering. Artificial tears and ointments must be applied to the eyes regularly to prevent dryness and irritation.

Pseudosyndactyly may occur. The development of squamous cell carcinoma of the skin is uncommon but may occur; therefore, individuals with JEB should be evaluated annually by a dermatologist. Other types of skin cancer do not occur in association with Severe JEB. Osteopenia/osteoporosis has been reported in patients with JEB and may be due to malnutrition and malabsorption problems as well as decreased mobility and weight-bearing activities. Because of the severe involvement of the skin and internal organs, there is a significant risk of overwhelming infection (sepsis), malnutrition, dehydration and electrolyte abnormalities, tracheal occlusion and death during the first two years of life.

Intermediate JEB

Intermediate JEB (previously Non-Herlitz JEB) generally is less severe than severe JEB.

- Generalized intermediate JEB, which may be caused by mutations in the collagen XVII gene or the laminin-332 gene
- Llocalized intermediate JEB, which is caused by mutations in the collagen type XVII gene

Generalized intermediate JEB presents at birth with widespread blistering and erosions. Blistering usually is worse in periods of warm, humid weather. Milia, scarring and nail dystrophy are common,

and mild keratoderma of the palms and soles may occur. Blistering on the scalp is common, and permanent hair loss (alopecia) may occur. Granulation tissue is rare. Poor dental enamel, oral erosions and dental caries are common, often necessitating extensive dental reconstruction. Poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract may occur, but with less frequency and, often, with less severity than is seen with Severe JEB. Laryngeal blisters and resultant scars cause a hoarse cry during infancy, and a hoarse, husky voice may remain through adulthood. Tracheal blisters may occur in individuals with intermediate JEB, and, if they occur when the affected person is an infant with a relatively small trachea, they may cause occlusion of the trachea and suffocation if not recognized and treated.

Osteopenia/osteoporosis has been reported in patients with JEB, and may be a result of malnutrition and malabsorption problems as well as a decrease in mobility and weight-bearing activities. Pseudosyndactyly does not occur. The development of squamous cell carcinoma of the skin is possible; individuals with JEB should be evaluated annually by a dermatologist. Other types of skin cancer do not occur in association with Intermediate JEB.

Localized intermediate JEB presents at birth with fewer, more localized blisters and erosions. Milia, scarring and nail dystrophy are common. Granulation tissue is not seen. Poor dental enamel, oral erosions and dental caries may be seen. Poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract are not seen. Pseudosyndactyly does not occur. The development of skin cancer is no more likely associated with Intermediate JEB.

JEB with Pyloric Atresia

JEB with pyloric atresia is caused by mutations in the **α6β4 integrin gene.** It presents at birth with widespread blisters and erosions. Although milia are not common, scarring and nail dystrophy frequently are obsverved. Congenital localized absence of skin and ear malformations have been reported. Oral erosions may occur, and dental enamel hypoplasia and dental caries may be more common. The key feature is the presence of pyloric atresia.

Pyloric atresia is the presence of a stricture or narrowing in the stomach at the pylorus, a muscle, that prevents stomach contents from passing into the intestines. Affected infants develop abdominal distention, vomiting, dehydration and electrolyte abnormalities within the first few weeks of life, and death is possible if pyloric atresia is not recognized and treated promptly through surgery.

Diagnosis may be aided by an ultrasound or contrast-enhanced X-ray such as an upper gastrointestinal barium study. Abnormalities of the genitourinary tract also have been reported. Other systemic findings such as poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract and eyes are not seen. There is no increased risk of skin cancer.

Other JEB Subtypes

JEB inversa, late onset JEB and larygo-onycho-cutaneous syndrome are caused by mutations in the laminin-332 gene. JEB inversa presents at birth with erosions localized to intertriginous areas such

as the groin, neck and axillae. Although milia are not common, scarring and nail dystrophy frequently are observed. Oral erosions may occur, and dental enamel hypoplasia and dental caries may be more common. With the exception of pyloric atresia, which may occur, other systemic findings such as poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract, genitourinary tract and eyes are not seen. There is no increased risk of skin cancer.

Late-onset JEB, also known as EB progressiva, typically presents after childhood with blisters and erosions. Nail dystrophy is common, but milia and scarring typically are not seen. Increased sweating (hyperhidrosis) and absence of fingerprints (adermatoglyphia) are reported. Oral erosions and dental enamel problems may be seen, but there does not appear to be an increased incidence of dental caries. Affected persons typically do not develop poor growth, anemia or problems with the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract. There is no increased risk of skin cancer.

Laryngo-oculo-cutaneous syndrome (LOC), or Shabbir's syndrome, presents at birth with blistering and erosions that typically favors the head and neck. Nail dystrophy and granulation tissue commonly are observed, while milia and scarring are less common. LOC is predominantly reported in the state of Punjab, India. Oral erosions, dental enamel problems, dental caries, and ocular (eye) erosions and other complications are common. Laryngeal erosions and related complications are a key feature and may lead to airway obstruction and death. Growth retardation and anemia may occur, but problems with the intestines/gastrointestinal tract or genitourinary tract have not been reported. There is no increased risk of skin cancer.

Dystrophic EB

Dystrophic EB, also called dermolytic EB, is caused by a mutation in the collagen VII gene. Generally, this mutation decreases the ability of the anchoring fibrils to hold together the layers of the skin. The degree of skin fragility depends on the degree of abnormality of the anchoring fibrils.

There are two main subtypes of dystrophic EB, dominant dystrophic EB (DDEB) and recessive dystrophic EB (RDEB), and several minor subtypes. The various subtypes of RDEB vary in severity. The disorder may be so mild as to only present an inconvenience to the affected individual or so severe that it is life-altering. National EB Registry data suggests that family members often have similar clinical presentations. Although there always are individual differences, the majority of family members tend to look alike in regard to their EB.

Dominant Dystrophic EB

Dominant dystrophic EB is transmitted as a dominant trait, while recessive dystrophic EB is a recessive disorder. In DDEB, only one parent also has DDEB. The affected parent has one abnormal copy of the involved collagen VII gene and one normal copy of the collagen VII gene (humans have two copies of most genes). With each pregnancy, there is a 50-50 chance that the abnormal gene will be passed along, resulting in a child with DDEB Likewise, there is a 50 percent chance that the normal gene will be passed to the child, resulting in a child who does not have EB (Figure 2).

Rarely, a child affected with DDEB may not have an affected parent; this is known as a *de novo*mutation, which means that the mutation occurred in the egg or sperm before fertilization and is not carried by either parent. RDEB is transmitted in an autosomal recessive form, in which both parents are normal without any manifestations of EB; however, each carries an abnormal copy of the keratin gene. In this instance, there is a 25 percent chance that the child will inherit both abnormal collagen VII genes, in which case the child will be affected.

In dominant dystrophic EB, blistering may be present at birth and may be widespread, as is seen in Intermediate DDEB, or blistering may occur mostly on the hands and feet in Localized DDEB. Congenital localized absence of skin (also called aplasia cutis congenita or Bart's syndrome) may be present at birth. Other variants include Localized DDEB, where blisters occur predominantly on the hands, feet, nails and lower legs and develop at birth or during infancy; DDEB with nail dystrophy only, which presents at birth or during infancy; and DDEB pruriginosa, which presents during childhood with either widespread, generalized blisters or with more localized blistering of the hands and feet in association with severe pruritus (itching) and nail dystrophy. In all form of dystrophic EB, scarring, nail dystrophy and milia are common. Granulation tissue is not seen. Poor dental enamel and oral erosions are not seen, although increased frequency of dental caries and constipation are reported with pretibial DEB. Poor growth, anemia, and blistering and other problems involving the trachea/respiratory tract, intestines/gastrointestinal tract, eyes or genitourinary tract are not seen. Pseudosyndactyly does not occur.

The risk of skin cancer is not increased in association with DEB with the exception of DEB pruriginosa, in which squamous cell carcinoma of the skin has been reported to occur after 30 years of age. A rare variant, DEB-bullous dermolysis of the newborn (DEB-BDN), presents at birth or during infancy with generalized blistering. Milia, scarring and nail dystrophy are common, as are dental caries. In some children with DEB-BDN, blistering stops in infancy.

Recessive Dystrophic EB

Recessive dystrophic EB (RDEB) is divided into several subtypes. The most severe subtype is Severe RDEB, previously known as Hallopeau-Siemens, which presents at birth with widespread blistering and is a chronic, progressive disorder. Milia, scarring, alopecia and other scalp abnormalities are common. Nail dystrophy with permanent loss of nails also is common. Severe blistering of the mouth may occur, and as the blisters on the oral mucosa heal, scars form and contribute to microstomia (small mouth opening) and ankyloglossia (tongue scarred to the floor of the mouth). Another contributing factor of microstomia is the scarring that develops on the outside of the mouth, further reducing the size of the mouth opening. Although dental enamel is normal, excessive dental caries occur. Fragile oral mucosa and microstomia make it difficult and painful to perform oral hygiene, and reduced production of saliva due to the injured mucous membranes creates dryness that leads to further decay; thus, regular dental cleanings and fluoride applications may be required every three months for severely affected individuals. Poor growth, anemia, and blistering and other problems involving the intestines/gastrointestinal tract and eyes cause significant problems.

The etiology of anemia in RDEB is complex, and includes iron deficiency anemia, chronic inflammatory anemia and nutritional anemia. Chronic blood and iron loss from skin; poor absorption

of iron and other nutrients due to chronic inflammation in the intestines; chronic infection; bone marrow suppression; deficiency of B-complex vitamins, vitamin C, vitamin E and selenium; and decreased red blood cell survival contribute to chronic anemia, which often is refractory to treatment. Growth retardation largely is due to the increased need for calories and protein required for healing wounds, the mechanical difficulties of eating created by the oral and esophageal scarring and the absorption problems created by the interruption in the integrity of the small intestine. Placement of gastrostomy feeding tubes often is indicated. Painful blisters and erosions may develop on the conjunctiva of the eye.

Symblepharon (adherence of the eyeball to the eyelid) also may occur. Involvement of the genitourinary tract is uncommon, and involvement of the trachea/respiratory tract does not occur. Pseudosyndactyly leads to mitten deformity of the hands and feet.

Severe RDEB is associated with an increased risk of squamous cell carcinoma of the skin and, less commonly, of malignant melanoma by 30 years of age; therefore, individuals with RDEB should be evaluated annually by a dermatologist. Renal (kidney) problems may occur, including glomerulonephritis, renal amyloidosis, IgA nephropathy and chronic renal failure. Other reported complications include cardiomyopathy, delayed puberty and osteopenia/osteoporosis, the latter of which may be due to malnutrition and malabsorption problems as well as a decrease in mobility and weight-bearing activities.

Other Recessive Dystrophic Subtypes

Intermediate RDEB (previously known as non-Hallopeau Siemens) also presents at birth with generalized blistering, and milia, scarring, alopecia, and other scalp abnormalities and nail dystrophy are common; however, other manifestations, including blistering of the mouth, anemia, growth failure, pseudosyndactyly, gastrointestinal and eye problems appear milder. Squamous cell carcinoma of the skin still may occur in early adulthood.

Other subtypes of RDEB include RDEB inversa and RDEB localized.

RDEB inversa presents at birth with blistering typically confined to intertriginous areas such as the axillae (under the arms), under the breasts, the neck and in the groin areas, and hands and feet, the chest and the lower back. Milia, scarring and nail dystrophy are common. Oral (mouth) blisters may be severe and may result in scarring with microstomia. Although dental enamel is normal, dental caries are common. Anemia and growth failure may occur, and involvement of the intestines/gastrointestinal tract and genitourinary tract may be severe with the development of esophageal, anal and urethral strictures. Females with RDEB inversa report vaginal scarring. Stenosis (narrowing) of the external auditory (ear) canal has been reported. Involvement of the eyes and the trachea/respiratory tract does not occur. Partial pseudosyndactyly may occur. Predisposition to skin cancer does not occur in association with RDEB inversa.

RDEB, localized presents at birth or in infancy with blistering confined to the lower legs, fingers and toes. Milia, scarring and nail dystrophy are common, and oral blisters may occur, but, otherwise, there are no associated systemic complications.

Kindler Syndrome

Kindler syndrome is a rare subtype of EB caused by mutations in the kindling-1 gene. It is an autosomal recessive disease that usually presents during infancy with blistering confined to the hands and feet in association with photosensitivity, or extreme sensitivity to sunlight with tendency to sunburn.

With age, skin blistering often improves, but photosensitivity does not, resulting in skin discoloration (lightening and darkening) with thinning and wrinkling and the appearance of small, superficial blood vessels (telangieactasia). Together, these features are called poikiloderma, and they occur most commonly on the hands and feet. Frequent dental caries and periodontitis with gingivitis are common. Involvement of the intestines/gastrointestinal tract, eyes and genitourinary tract may occur. Keratoderma of the hands and feet, nail dystrophy and pseudosyndactyly have been reported. The development of squamous cell carcinoma of the skin appears to be more common.