TESTIMONY OF

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"Providing a Parent Perspective of Having a Child with Recessive Dystrophic Epidermolysis Bullosa and How to Facilitate Treatments and a Cure"

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HEALTH, EDUCATION, LABOR AND PENSIONS

Regarding

"TREATING RARE AND NEGLECTED PEDIATRIC DISEASES: PROMOTING THE DEVELOPMENT OF NEW TREATMENTS AND CURES"

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I would like to thank Chairman Harkin, Ranking Member Enzi, Senator Brown and the entire committee for allowing me to speak today on behalf of the children, and their families, who suffer from Epidermolysis Bullosa, also known as EB. I would also like to thank the members of the committee who supported Senate Resolution 180 in 2006, which established National EB Awareness Week. Specifically, I would like to thank Senator Hatch, who was a co-sponsor of this resolution. S. Res. 180 passed the Senate by unanimous consent and without amendment. With your continued support, we can transform EB into a treatable and curable disease. I would also like to recognize Megan Barron, Joella Murray and Leandro Santos who are in attendance today. These individuals all suffer from EB. They endure more pain than one can imagine. Their burden, one that no child or person should face, inspires us to do what we must – cure this disease.

What is Epidermolysis Bullosa (EB)?

EB is a debilitating and devastating genetic disorder that affects a child from the moment he or she is born. EB is not specific to any ethnicity or gender. A child who suffers from EB lacks the critical protein that binds his or her layers of skin together. This protein acts as the "velcro" that attaches one layer of his or her skin to the other. Without this "velcro" when this child moves, his or her skin slides apart, blisters and shears off leading to severe pain, disfigurement, and in too many cases, a premature death from an aggressive form of skin cancer called Squamous Cell Carcinoma. Within certain subsets of EB, the cumulative chance of developing this cancer is almost 100%. A child with a severe form of EB can have a 60% cumulative risk of dying by age 15. There are three major EB subtypes – Simplex, Junctional and Dystrophic and within each type there are multiple subsets. The difference among them is the level at which a blister forms within the skin and which particular protein is missing or impaired.

My experience with EB began on October 11, 2007. On that day, my wife Jamie and I were blessed with the birth of our beautiful son Jackson, who is the light of our lives and a joy to everyone around him. Yet, our lives were nearly shattered with the diagnosis that Jackson was born with a form of EB called Recessive Dystrophic EB (or RDEB for short). Despite being born at a major metropolitan hospital, the physicians caring for Jackson had never seen a case of RDEB before, which made his condition difficult to diagnose, an experience most EB children share. RDEB is considered to be one of the worst forms of EB. Jackson, like all those with RDEB, is missing the protein Collagen VII. This became evident on the day after Jackson's birth, when nurses removed a band-aide from his newborn left heel and the adhesive tore off his precious skin. Most of my comments will focus on RDEB, although there are equally horrific forms of EB which share many characteristics with RDEB.

Like most people, I had never heard of EB and had no awareness that our son would suffer from this condition until he came into this world. We did not know about EB because it is an orphan disease, which is defined as a disease affecting fewer than 200,000 people. Figures from the National Institutes of Health estimate that between two and four out of every 100,000 children are born with EB. Based upon these figures, EB would be an "ultra-orphan" disease defined as a disease that affects fewer than 20,000 people in the United States. The government considers EB a "catastrophic illness." "Catastrophic" only begins to describe life with EB.

The Devastation of EB

To say that EB impacts every aspect of a child's life is a gross understatement. Skin is the body's largest organ. Among its most important functions, skin is the first line of defense to protect the body from trauma and infection. Everything we do in life impacts our skin – walking, eating, playing, sitting, writing, hugging, sleeping – the list goes on. For children with EB – like our son Jackson – every aspect of their lives at every moment is overshadowed by this terrible disorder. These children are often born missing large areas of skin leaving gaping wounds that never

heal; walking and standing are impaired over time because their toes become fused as the result of continuous injury; the simple joy of holding a crayon to draw becomes impossible because their fingers fuse and contract turning their young hands into mittens; eating is painful and sometimes impossible because the esophagus closes due to injury and scarring, which is only temporarily reprieved by a surgical procedure in which the esophagus is stretched open. When this solution stops working, a gastric feeding tube is placed in their small bellies in order to enable proper nutrition and hopefully stave off growth retardation and anemia. Even the fundamental act of sleeping is extraordinarily difficult because of the level of pain and discomfort that these children experience 24 hours a day.

Like all kids, children with EB rub their eyes when they are sleepy. Only in their case, rubbing their eyes can tear their eyelids and corneas, prohibiting these children from opening their eyes in the morning without suffering extreme pain. Naturally, children with EB also want to play alongside their peers. However, falling down on the playground can remove all the skin from their little palms or produce a blisters on their knees the size of oranges. Respectfully Senators, please take a moment and imagine yourself, your son or your daughter, or a relative being one of these innocent and helpless children – slowly and painfully having your little body transformed into one devastated by infected open wounds, blisters and scarring. Imagine that the simple act of hugging your child could tear the skin off his or her body. This describes just a fraction of what these children experience, as it does not account for the social scrutiny and the stares they receive by simply walking or being wheeled down the street. In its entirety, EB impacts vision, speech, nutrition, mobility and indeed every single aspect of a child's life. Unfortunately, a recent study determined that approximately 50% of children with RDEB are *always* in pain.

During a typical day, a child with RDEB undergoes a special bath and a bandage change. Given the large areas of skin missing from such a child's body, bathing is an extraordinarily painful experience. Bandage changes can last anywhere from 30 minutes to several hours and bandages can cost a family as much as an astounding $14,000 per month. An EB child's meals consist mostly of soft foods and liquids, assuming he or she has not been forced to resort to receiving nutrition through a feeding tube. When skin blisters or tears, it must be treated as soon as possible, causing parents to carry a costly arsenal of needles and bandages anytime that they leave the house. For a child with EB, the joyful act of participating in sports – such as little league or youth soccer– is often out of the question due to the skin tears, blisters and scarring that would result. For this reason, even playing with other children can be impossible. Simply put, this disease prevents a child from just being a child.

Speaking for a moment as Jackson's dad, every morning Jamie and I wake up and hope that Jackson hasn't torn the skin off his neck and face from rubbing during his sleep. We hope he does not have a blister in his mouth or his throat that prevents him from eating that day. Throughout the day, we check his body for blisters that have developed and lance any with large needles when we see them. Sometimes this can be extremely painful to Jackson but we are forced to physically restrain our son and do it anyway. We dress him in special shoes and only soft clothing. We keep bacterial culture kits at home and use them all too often to check him for infection. Like many EB patients, our son must avoid crowded places that kids love such as zoos, museums and birthday parties. And we must stay indoors during the bulk of the summer because the heat and humidity exacerbates his blistering. Every day, Jackson takes a bath with vinegar or bleach to help kill the bacteria on his little body. This bath often causes stinging pain to Jackson's many open wounds. He sits patiently through his uncomfortable bandage changes; sadly, our little boy does not know any differently. He endures physical, occupational and feeding therapies as well as specialized nursing visits six times per week to keep his body as mobile and healthy as possible. And yet, through all these painful challenges that would cause most of us simply to give up, our brave Jackson's smile lights up a room even though his body is slowly being ravaged by this disease. Some additional examples: as noted above, our son lost all of the skin on his heel from the removal of a band-aid the day after his birth which has never grown back normally; his hands are severely scarred and the quality of his skin is poor due to the continuous damage they endure; that damage continues to progress up his arms everyday. It's critical to note that – despite the pain and discomfort I have just described – Jackson has a moderate case of RDEB. Children with more severe cases suffer exponentially more.

With this background, the key questions are (i) where are we now (ii) where can we can go and (iii) what is needed to succeed at giving these children the fundamental American right of a chance at living good lives.

Current EB Research and the Reasons EB Patients Continue to Suffer Needlessly

Perhaps the most hopeful aspect of EB today for Jackson, and all children living with EB, is the quality of research being performed in the United States and internationally that can render this disease livable and ultimately a disease of the past. Due to research dating as far back as 1974, which has been funded by NIH grants as well as private donations; EB is at a stage where treatments and cures have the potential, with your help, to become a reality. Indeed, researchers know exactly what causes this disease and have encouraging knowledge of how to fix it. But where we are failing is in marshalling the resources needed to get there. To reiterate, we are not at the beginning of this journey. Technology has caught up to the research and, with more funding, a finish line can be in sight for the thousands of children, like our son Jackson, who were born with this disease.

Some of the major areas of research currently being conducted in the United States include protein therapy by Doctors David Woodley and Mei Chen of the University of Southern California and Doctor Peter Marinkovich of Stanford University. The concept of this research is straightforward. EB researchers estimate that a person needs only 35% of the typical level of Collagen VII for the skin to behave normally. Drs. Woodley and Chens' concept is to replace the protein that is missing in RDEB kids – Collagen VII – with localized injections. Drs. Woodley and Chen have proven in a mouse model that this method works. They are now looking to commence a Phase I trial as soon as possible. Experts indicate that with the *sufficient resources*, a commercialized therapy could be available in five to eight years. Imagine what that would mean to a child whose skin tears off in her shoes to have a localized injection that renders the skin on her feet potentially normal. For years, doctors have administered localized injections of Collagen I for cosmetic purposes. Collagen VII and Collagen I are related. In this proposed treatment, the doctors would simply administer Collagen VII in a similar fashion as Collagen I is administered in a cosmetic setting. In other words, doctors have the knowledge to apply this treatment as soon as it is available. While not a cure, this would be a truly viable "game changing" treatment, allowing a child like my son to live a better life.

Other potential cures are being pioneered both at the University of Minnesota and at Columbia University by Drs. Wagner, Tolar, Christiano and Cairo. These are stem cell therapies and the basic concept is to replace the bone marrow of an individual with EB with a donor who has the proper Collagen VII production capability. As the body's wounds heal and the skin regenerates, the theory is that Collagen VII would be produced, which in turn would keep an EB patient's layers of skin together. There are currently trials ongoing at both locations, which have shown promise as a systemic cure.

At Stanford University, Drs. Lane and Khavari have labored over a form of gene therapy to treat EB. In this approach, a small section of skin is removed from a person with EB and the gene "error" is corrected to produce Collagen VII. The corrected skin is grown into larger amounts and then grafted back onto the body. We hope that they can commence a trial very soon.

In addition to these efforts, internationally, there has been work by Dr. John McGrath in the United Kingdom in which individuals with EB received injections of donor cells that produce Collagen VII. Results, though early, have been promising.

So why hasn't Collagen VII been developed commercially? Given that its unquestionably important life saving purpose? The answer is that the target market of EB children is not large enough to attract commercial interest on

its own. Development costs – which can run into the hundreds of millions of dollars – trump the profit that can be made. Simply said, the economics do not work in most cases – and children like our son Jackson are the victims of this unfortunate and unfair fiscal reality. When curing a disease devolves purely into the mathematics of how many children are afflicted with EB versus the profit potential of developing this attainable treatment for these children, we have gone astray from our fundamental American values. As I described earlier, there are real therapies and treatments in the works that – with appropriate funding – can offer these children suffering from EB a chance at a "normal" life. What keeps these children in bandages is the lack of funds, the difficulty in attaining any funds that may exist and the cumbersome approval process of potential treatments.

What is Needed to Beat EB and Save America's Children

I believe the solution must be one of a combined effort between the public and private sectors. For EB children to have chance at a life free of pain – one where they can "truly" be kids – they need more available funding for researchers, more incentives to fund this research via a public/private partnership, an approval process that considers both safety as well as the devastating effects of EB, and finally a mechanism to ensure the treatments are affordable to those who need them.

The National Organization for Rare Disorders (NORD) estimates that there are 7,000 rare diseases affecting 30 million Americans. Of these disorders, only approximately 200 have FDA-approved treatments. Less than 3% of these diseases have treatments available. According to figures provided by the NIH, it provided only $118 million in research funds for orphan drugs out of its $30 billion budget in 2009. Unfortunately, this amounts to 0.3% of the NIH budget. The Office of Orphan Drug Development provides approximately $15 million annually in grants. Assuming there is additional funding via other federal sources, it may be safe to assume that approximately $500 million in federal funding per annum is available for orphan diseases. To put this in context, Genzyme, a biotechnology company, estimates that it cost over $500 million to develop a treatment for a rare disorder called Pompe disease. It also means that of the 10% of the U.S. population affected by rare diseases, roughly $16 per person is spent per year in searching for cures. *ONLY $16.* The United States federal budget is $3.5 trillion. Of that amount, the 2010 budget calls for $3.4 billion to support carbon capture and storage technology. Investing in the future of American energy is very important. But it begs the question; shouldn't investing in the future leaders of America – including our son and the many other bright young stars afflicted with this horrible disease – be at least as important? Given the current economic environment, I understand as well as anyone that there is little room for additional spending and we have many pressing issues at hand. It is a question of what our priorities should be as Americans who value human life and the right to have a "normal" and carefree childhood.

The government cannot provide the solution itself, nor should it be expected to. However, for a disease that – although devastating and debilitating – affects too few people to spark commercial interest, the government must lead and provide incentives for private development of drugs and therapies. The proposed priority voucher program encouraging drug development for rare pediatric diseases, which is a refinement of the tropical disease voucher program, is a fantastic example. If this program is expanded to cover rare pediatric diseases, then a company that would not otherwise focus on orphan drug development will do so because it can enjoy commercial benefit while also serving a social good. This would bring additional solutions to the market quickly, which would help every child with EB and indeed any other rare disease. Corporations will follow the government's lead. Public interest, awareness and incentives can shape private behavior. Creative solutions that provide direct or indirect incentives are effective and indispensable methods to spur the pace and likelihood of treatment developments. I – along with all other parents of sons and daughters suffering from rare diseases – urge you to consider the proposed priority voucher program. This program can improve and save the lives of millions without costing the taxpayers anything.

Beyond additional funding and private market incentives, the process for the approval of rare disease therapies must be streamlined. Achieving the delicate balance between the safety of treatments (particularly new or developing treatments) and the devastation of rare diseases remains a tremendous challenge for regulators. We need a process which deeply considers the alternative that individuals with EB or other orphan diseases face in lieu of approved treatments. A child with RDEB lives each day with tremendous pain, hoping his fingers and toes do not fuse and his esophagus does not close. With this disease, every breakdown is one step closer to a terminal cancer. Because of the horrific symptoms of this disease, individuals with EB and the parents of children with EB are more willing to accept risks that may be inherent in emerging therapies because the alternative is a painful and debilitating life. I am not advocating that safety be cast aside. I am saying that a person with EB defines safety differently than a healthy person; to a person with EB, simply living life is inherently unsafe. The CureTheProcess campaign by the Kakkis Foundation has promising ideas on how to address this issue. CureTheProcess suggests that the FDA create a new review division for rare biochemical diseases; and for the FDA to issue new guidelines to give the rarest diseases access to the accelerated approval process. We can quickly and dramatically improve the current regulatory process for rare diseases. The result should be a surge in development activity for even the rarest disorders. An improved regulatory path working together with the NIH TRND Program, Cures Acceleration Network and other new incentive programs will help ensure more patients with rare disorders will get earlier access to specific, effective treatments.

These potential treatments for which we seek funding must also be made affordable to those who need them most. A cure for EB is useless to the child shut out because he or his family cannot afford to pay for it.

One additional area that is often overlooked is that treatments for rare diseases often lead to discoveries with much wider applications. For example, Remicade – which was developed for the treatment of Chron's disease, a population of 500,000 people – has been found to effectively treat Rheumatoid Arthritis and forms of Psoriasis, a population over 5 million people. Rituxan, developed for non-Hodgkin's lymphoma – a group of 70,000 people per year now helps the 1.3 million Americans who suffer from Rheumatoid Arthritis. Epogen, now used for Anemia, is another illustration.

As these examples demonstrate, funding of orphan diseases can frequently have the unintended consequence of benefitting a much broader population than those suffering from the orphan disease itself. By devoting the resources to protein, stem cell and gene therapies to combat EB, we may also indirectly aide many other Americans. This potentially includes brave veterans who have suffered burns that resulted in blistering and scarring while serving our country on the battlefield, as well as victims of other burn injuries. These individuals share many characteristics with severe RDEB children. EB is worthy of curing in its own right, but many Americans (including many of America's Finest; the men and women of our military) could benefit along the way.

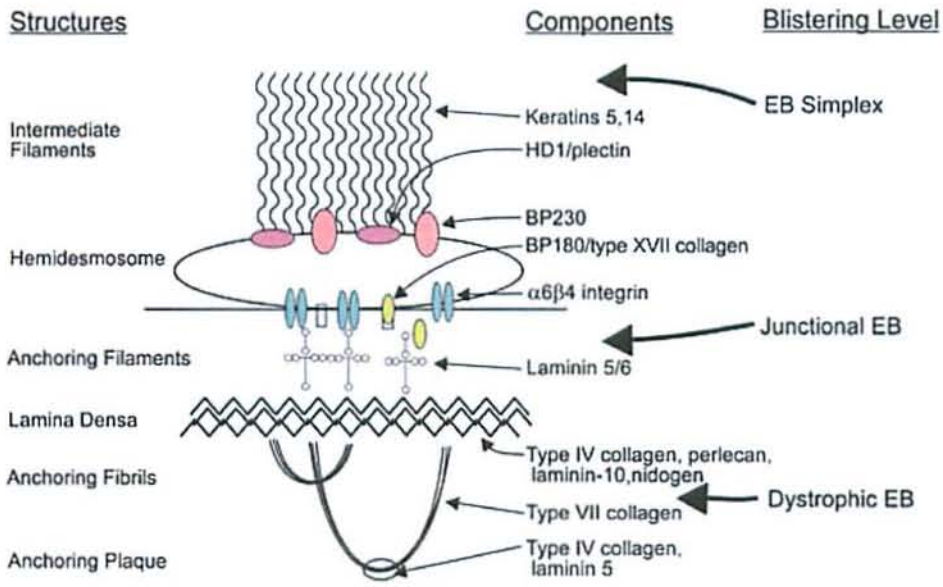
Conclusion

In closing, while there is promising research focused on helping children with EB, the current system fails them. It does not provide enough funding, sufficient private market incentives or a review process that is appropriate for the severity of the disease. The solutions are clear – more public and private funding and partnerships, a streamlined and accelerated review process and affordable treatments. We know the solutions and now, with this committee's help and support, Jackson, Joella, Megan, Leandro and every child with EB can grow up to live healthy and pain-free lives. But only if we give them that chance. Inaction is not a choice. This can be done. We can cure this disease. Let's turn hope into reality, and let's do it now. Thank you for inviting me to testify today.

Appendix:

I. Forms of Epidermolysis Bullosa[1]

There are three main forms of EB: EB Simplex, Junctional EB and Dystrophic EB. These different subtypes are defined by the depth of blister location within the skin layers. Blister formation of EB simplex is within the epidermis. Sometimes EB simplex is called epidermolytic. Blister formation in Junctional EB is seen at the level of the lamina lucida within the basement membrane zone. Dystrophic EB or dermolytic EB is a scarring form of EB which occurs in the deeper tissue at the level the lamina densa or upper dermis.



EB Simplex is caused by faulty proteins in the top layer of skin. This results in incorrectly formed keratins, deeming them unable to perform their normal role as a 'scaffolding' for the top most layer of skin. The top layer of skin falls apart, resulting in a blister. Although EB Simplex is considered a non-scarring form of EB, secondary infection may cause scarring.

Junctional EB is caused by mutations in the genes encoding alpha 6, beta 4 integrin, collagen XVII or one of the three chains of Laminin 5. This leads to defects in the formation of hemidesmosomes or anchoring filaments. Defects within any of those components of the skin allows for the separation of tissue and blister formation whenever there is friction or trauma to an area. In many instances blistering can occur spontaneously.

Dystrophic EB is caused by mutations in the genes that carry the instructions necessary to produce the proteins in the basement membrane zone of the skin. This results in incorrectly formed anchoring fibrils, deeming them unable to perform their normal role as a 'stable interweave' between the dermal and epidermal layers of the skin. Mutation occurs within the collagen VII gene, which encodes the protein of the anchoring fibril. Anchoring fibrils hold together the two layers of skin. As a result, there is a lack of adherence and disruption of the skin when any friction or trauma occurs to an area. Where the two layers separate there is a blister. Blistering in the various types of dystrophic EB causes scarring.

[1] Dystrophic Epidermylosis Bullosa Research Association of America (DebRA)

To differing degrees, EB can manifest itself in the following ways:

- Generalized blistering
- Growth retardation and malnutrition
- Gastrointestinal tract - may include blisters in mouth, esophagus and/or anal margins
- Pseudosyndactyly - Fusion of fingers and/or toes
- Problems with the soft tissue inside the mouth leading to esophageal strictures
- Squamous Cell Carcinoma
- Ocular (eye) involvement
- Atrophic scarring - depressions in skin as a result of thinning in epidermis or dermis
- Nail dystrophy - presence of rough, thickened or absent finger or toenails
- Presence of Milia - tiny skin cysts
- Anemia - a reduced amount of red blood cells, volume of red blood cells and amount of hemoglobin
- Granulation tissue - appearance of red fleshy tissue which is capillary formation during tissue healing
- Dental caries (cavities)
- Enamel hypoplasia - underdeveloped enamel upon the teeth
- Genitourinary tract involvement including scarring and/or urethral stenosis
- Scalp abnormalities - presence of blisters on scalp and/or scarring alopecia (areas of scarring with absence of hair growth)
- Respiratory tract involvement