TOUCH-ME-NOTS

Children with epidermolysis bullosa can blister at a touch. While a cure remains elusive, much is being learned about the condition itself.

By JOANNE SILBERNER

Ten years ago at Montefiore Hospital in New York, pediatric intern Lawrence Schachner was called in to treat a newborn boy with a peculiar problem. "I saw a baby with a massive number of blisters and skin erosions," he recalls. Efforts to help hurt the infant instead. "In trying to care for the baby I found that very little mechanical trauma [physical disturbance] added up to a whole lot of skin lesions, which made the baby vulnerable to infection."

Attempts to put in an intravenous line to supply much-needed extra nutrition resulted in more trauma to the skin, and more blistering, not only to the skin but also in the esophagus. "I was losing a situation I thought I should be winning," Schachner, now at the University of Miami, says.

The baby eventually died, a victim of epidermolysis bullosa (EB), a disease once called epidermolysis lethalis because it was thought to be fatal in all cases. In the 10 years since Schachner saw his first EB patient, great strides have been made in defining the biochemistry and genetics of the disease, which is inherited in many cases, and researchers believe this knowledge may eventually lead to a cure.

Today at least 18 different diseases — most of which can be survived with proper care — fall under the heading of EB. All of the diseases are marked by a lack of cohesion between or within the layers of the skin. In some cases the mucous membranes are also affected. "As our probes become more specific the number of syndromes [identified] will become even larger," predicted one EB researcher at a recent Washington, D.C., conference on the EB-linked diseases and their therapies. The conference was sponsored by DEBRA (Dystrophic Epidermolysis Bullosa Research Association), a Brooklyn-based group that provides assistance and advice to EB victims and their families and finances EB studies.

The effects of EB range from mild blistering on the hands and feet associated with hot weather to fatal blistering in major organ systems. Typical EB blisters resemble serious burns and have to be dressed several times a day. Many of the victims suffer frequent infections and rely on antibiotics.

Estimates of sufferers in the United States range from 10,000 to 50,000; a registry under consideration by the National Institutes of Health may soon give a better idea of the number of victims. The diseases, which strike across races and nationalities, in most cases become apparent at an early age.

The skin consists of two layers: the outer layer, or epidermis, and the inner layer, or dermis. The epidermis serves primarily as a protective covering, while the fibers and cells of the dermis are laced with blood vessels and nerves, and are embedded with hair follicles, sebaceous (oil) glands and sweat glands.

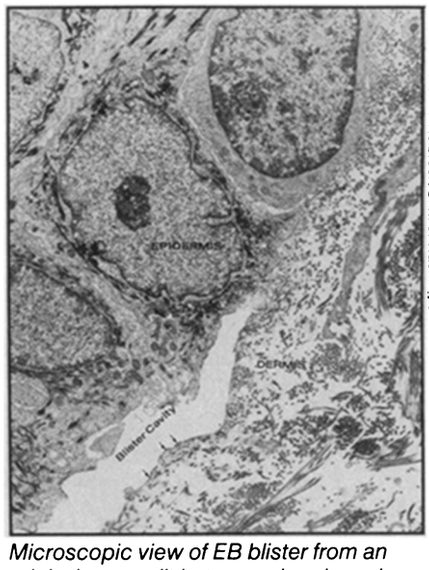
Some types of EB involve just the skin. Others also affect the nails, esophagus, respiratory tract, eyes, digestive system, urinary tract, even the enamel of the teeth. In one form, the ends of the fingers or toes fuse together, webbed in by scarred skin. The limb ends look like cocoons.

Children with EB, many of whom were in attendance at the meeting, are otherwise normal, but they have some great hurdles to face: overcoming the disgust of their peers and the public, and protecting their sensitive skin without becoming isolated from the world. Rochelle Eisenberg, an Australian social worker who has a son with EB, notes, "The child comes to associate human contact with pain. But they have a closer involvement with the family, because of the demanding nature of the illness."

The weak connection in the skin can occur within the dermis or epidermis, or between the two layers. Diagnosis is accomplished by rubbing the skin gently and taking a tissue sample of the blister that forms within a few minutes. In patients with less sensitive skin, suction is used to raise a blister.

Then the fresh blister biopsy is looked at with an electron microscope, or the newer technique of immunofluorescence. In immunofluorescence, antibodies to three skin components are added to the tissue. A second set of antibodies that will react with the first set and that have been saddled with fluorescent molecules is added. The result is checked in a microscope equipped with a light source capable of exciting the fluorescent molecules.

The blister's location in relation to the three antibodies is checked — if all three antibodies are at the base of the blister, then the EB is one of the types that occur within the epidermis. If they're at the roof, it is dystrophic — within the dermis. And if one is on top, with the others on the bottom, the patient has junctional (between skin layers) EB.



Photos: Karen A. Holbrook/Univ. of Washington

Microscopic view of EB blister from an adult shows split between dermis and epidermis. Arrows point to lamina lucida layer, normally sandwiched between the two.

Within these three types of EB, some of the diseases are now known to be inherited in a recessive pattern, so that only children who inherit abnormal genes from both their mother and father will get the disease. Other forms are dominant, meaning only one gene is necessary. Still other cases arise from a first-time mutation, and some of these patients have an excess of immune system components in their skin.

While EB has been diagnosed prenatally by taking a skin biopsy from the fetus, the procedure is difficult and risky. Researchers are presently searching for something sloughed off into the amniotic fluid that marks either EB or its absence so that diagnosis could be accomplished with the more routine amniocentesis.

With the patterns of inheritance for the most part figured out, focus is now being switched to what is happening at the molecular level, with the long-term goal of putting a stop to it. "Identification of those abnormal genes that permit blistering will make antenatal diagnosis simpler," says Joseph McGuire of Yale University in New Haven, Conn. "The next step, the correction of the identified defect, is not so simple."

The key player in EB is believed to be collagen, a class of proteins that serve as the major structural component of the body. Collagen is not a simple system — there are many types, and each, noted one scientist at the conference, "is synthesized by different kinds of cells, and regulated by a variety of different factors."

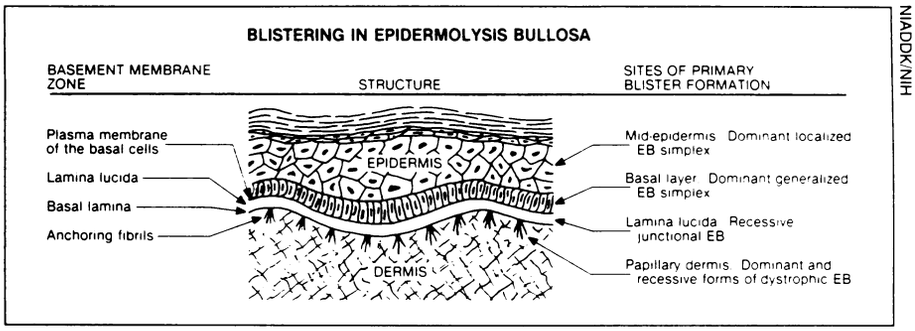
Explains Robert Briggaman of the University of North Carolina in Chapel Hill, "Some of these [collagen] structures may not be made properly, or there may not be enough of them. Some of them may be prematurely broken down."

Research has zeroed in on anchoring fibrils — tiny structures stretching between the dermis and epidermis, believed to be made of collagen. In the past few years, Briggaman and others have isolated antibodies to the fibrils; those antibodies, along with an antibody against a particular form of collagen, are enabling a closer look at what is awry.

The cascade of enzymes that break down collagen is also being investigated; among them is chymase, an enzyme that activates collagenase, which destroys collagen. "This [chymase-initiated breakdown] is a natural process that goes on all the time in normal individuals," says Mark Eisenberg of the University of New South Wales in Australia. But in certain EB victims, he has found, the process is much more active.

"As yet we have no evidence that [an excess of] the enzyme is responsible for skin fragility," he says. If this becomes known, he observes, "then a whole host of pharmacological agents that act on cells that produce chymase will become useful in treating EB."

For the moment, though, treatment is strictly palliative — dressing the wounds, ensuring proper nutrition, treating infections and giving psychological support. There have been glimmers of hope. A couple of years ago a study indicated that retinoids (a class of chemicals that includes vitamin A) inhibit the activity of proteins that break down collagen, but results of a trial at Washington University in St. Louis weren't good. While retinoids decreased the number of skin lesions, all of the patients exhibited side effects, including dry skin and itching — serious problems in EB patients.



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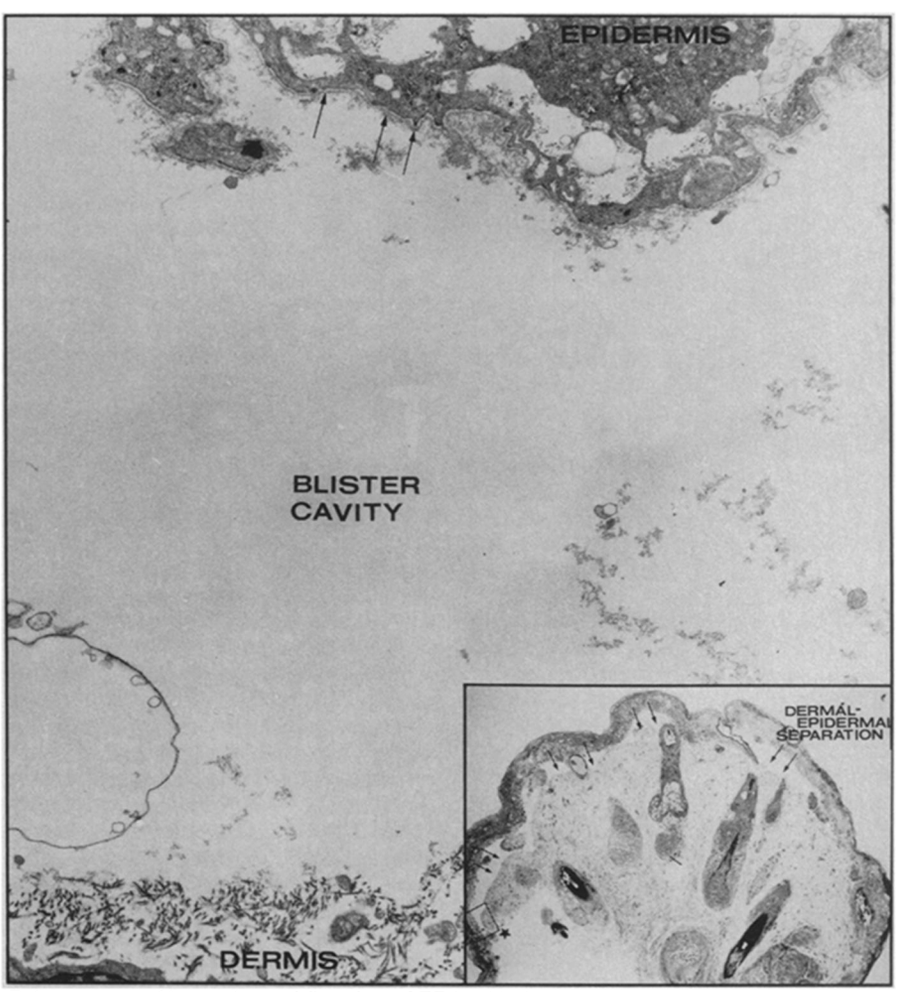
Researchers at the recent meeting were more hopeful about phenytoin (Dilantin), a drug presently marketed for use against epilepsy. The drug is known to inhibit the breakdown of collagen, and in initial trials it has been successful against recessive dystrophic EB. Researchers are attempting to recruit enough EB sufferers to evaluate it.

"Research is far ahead of treatment," notes Jo-David Fine of the University of Alabama at Birmingham, who has been working on monoclonal antibodies against skin components. But he is hopeful. "As we learn more biology and immunology about EB, that information will generate clever ideas of how to exploit drugs in treatment."

Observes Briggaman, "What needs to be done is to get into the way in which the genes are working. ... We're pretty well clear on the structural defects, and we're starting to understand the biochemistry.

"We're at the end of the beginning," he says. "But there's a long way to go yet." □



Enlargement of inset shows blistering of EB in skin from 19-week-old fetus.