RNA are all righties while the amino acids that make up proteins are all southpaws. That's a puzzle because both the sugars and amino acids are chiral molecules—that is, they can exist in two different, mirror-image forms. But not on Earth they don't. No one can satisfactorily explain how this "enantiomeric excess" came about on Earth. But Bonner can in space, he told his audience.

Bonner's scenario, developed with his Stanford colleague Edward Rubenstein, relies on the intense ultraviolet light that would emanate from electrons accelerated by the powerful magnetic field of a rapidly rotating neutron star. This synchrotron radiation would have strong circular polarization—that is, the plane of the waves would rotate continuously, in one direction for light coming from the star's northern hemisphere and in the other for light from the southern. If any interstellar grains bearing organic materials strayed into range, Bonner contends, the circularly polarized light would selectively destroy molecules of one handedness while sparing the other.

Biased by their encounter with the neutron star, the compounds could have reached Earth millions of years later, either in comets or in dust swept up as the solar system passed through an interstellar cloud. Such an extraterrestrial infusion could have sowed the seeds of today's curious asymmetry.

Chiral-molecule expert J.P. Ferris of the Rennselaer Polytechnic Institute is intrigued, but he points out uncertainties—among them the fact that no one has yet observed a neutron star giving off circularly polarized ultraviolet light. "It's a hypothesis, is what it really comes down to," says Ferris, but one he thinks is worth exploring. Interstellar-grain expert Greenberg is preparing to do just that in his laboratory at the University of Leiden. He plans to shine circularly polarized ultraviolet light on chiral compounds containing opposite-handed forms in equal amounts, trapped in simulated interstellar grains. He'll then analyze the grains to see if molecules of a particular handedness were destroyed preferentially.

And there's already some support for one of Bonner's assumptions: that an enantiomeric excess—however it originated—can survive for millions of years, protected by the deep cold of interstellar space. According to geophysicist Michael Engel of the University of Oklahoma and his colleagues, an organic-rich meteorite that landed in Australia in 1969 may contain a significant excess of one amino acid's left-handed form—perhaps a signature of an ancient encounter with a neutron star. ■ JOSEPH MARCUS

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A Layer by Layer Look at the Skin Blister Diseases

Discovery of the gene defects causing two types of hereditary blistering diseases is aiding understanding of skin structure

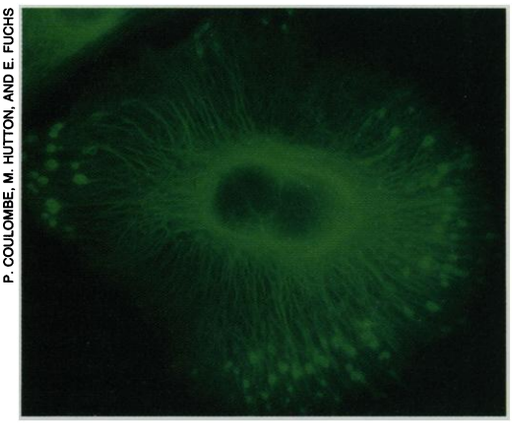
REAL EPIPHANIES ARE RARE IN SCIENCE. THE scene where a scientist solves a mystery and yells "Eureka" belongs more to the realm of science fiction than to fact. Less rare perhaps, but nevertheless breathtaking, are those discoveries that ripple out through a community of researchers, triggering a surge of new insights. Take the case of the rare hereditary skin diseases known as epidermolysis bullosa.

Called EB by the dermatology community, this family of diseases shares one aspect: They are all characterized by such an extreme skin fragility that even the slightest friction can cause painful blistering. Until very recently, no one understood the genetic basis of any form of EB. But within the past few months, three independent teams have identified the defects causing two forms of EB. And their discoveries are having the ripple effect: Not only are they pointing the way to potential new therapies for the blistering diseases, they may also have wider implications by producing a much better picture of skin structure, which has been as poorly understood as the EB diseases. Such information may, for example, provide new insights into normal skin aging.

Two of the teams, one led by Ervin Epstein Jr. of the University of California, San Francisco (UCSF), and the other by Elaine Fuchs of the Howard Hughes Medical Institute at the University of Chicago, are studying the commonest and least severe form of EB, known as EB simplex. While about 50,000 U.S. residents have some form of EB, how many suffer from EB simplex is unknown. Martin Carter, head of the National EB Registry's branch at Rockefeller University in New York, says, however, that roughly half of the 1700 tissue samples collected by the registry come from patients with EB simplex.

What these people experience stems from a defect residing in the outermost layer of the skin, known as the epidermis. Their epidermal cells, which are called keratinocytes, are unusually fragile and break apart when the skin is abraded. The cell breakdown leaves a gap in the epidermis, which can be filled with extracellular fluid to form blisters.

Fuchs and her colleagues hadn't initially set out to study EB. They were instead curious about the function of the keratins, a family of over twenty proteins that are found almost exclusively in the keratinocytes where they form networks of filaments. The structure of keratins has been studied for more than 20 years, Fuchs says, but little was known about their function back in the mid-1980s when her team began working on them.



P. COULOMBE, M. HUTTON, AND E. FUCHS

All balled up. *A mutant keratin gene results in abnormal keratin filaments, with ball-like structures at the ends, in this mouse cell, which was taken from a trangenic animal.*

One way to find out what the filaments do is to alter them by introducing mutations into one of the keratin genes, and then see what fails to occur, explains Pierre Coulombe, a postdoc in the Fuchs lab. And that's what led the group into the EB arena. The researchers discovered that the mutations caused the keratin networks in cells growing in culture to be disrupted, sometimes to such an extent that the keratin ended up clumped around the nucleus. To find out how the mutations might affect keratinocyte function in a living organism, graduate student Robert Vassar, Coulombe, Fuchs, and their colleagues then went on to insert mutant keratin genes into mouse embryos. The resulting transgenic mice developed a disease very much like EB. Says Coulombe: "The transgenic mice were missing significant portions of their skin. The skin was blistered either by the birth process or by trivial mechanical trauma."

Back at UCSF, meanwhile, the Epstein group had also gotten interested in the keratins, but for a different reason. They had noticed a resemblance between certain diseases of red blood cells and EB. Red blood

cells can become fragile because of mutations in the proteins making up the cell's filamentous web, and, says Epstein, "It occurred to us that there was some clinical similarity between the two diseases." He and his colleagues investigated a number of proteins in keratinocytes and when they came to the keratins, they hit pay dirt.

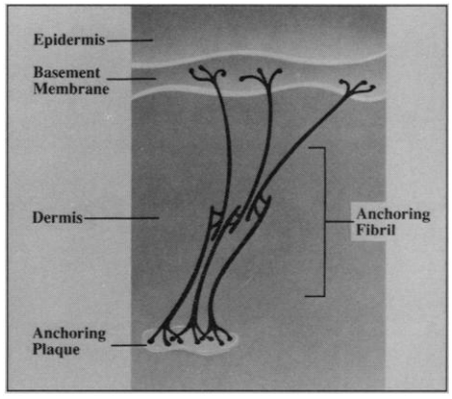
In this issue of *Science*, the Epstein group reports the results of genetic studies in which they have linked keratin gene mutations to EB simplex in two families with the hereditary disease (see page 1202). In one family the mutation is in the gene encoding keratin 5 and in the other it's in the gene encoding keratin 14. Data from the laboratories of E. Birgitte Lane at the University of Dundee in Scotland, Irene Leigh at the Imperial Cancer Research Fund in London, and Robin Eady at the Institute of Dermatology, also in London, provide additional evidence that these keratins are involved in a form of EB simplex.

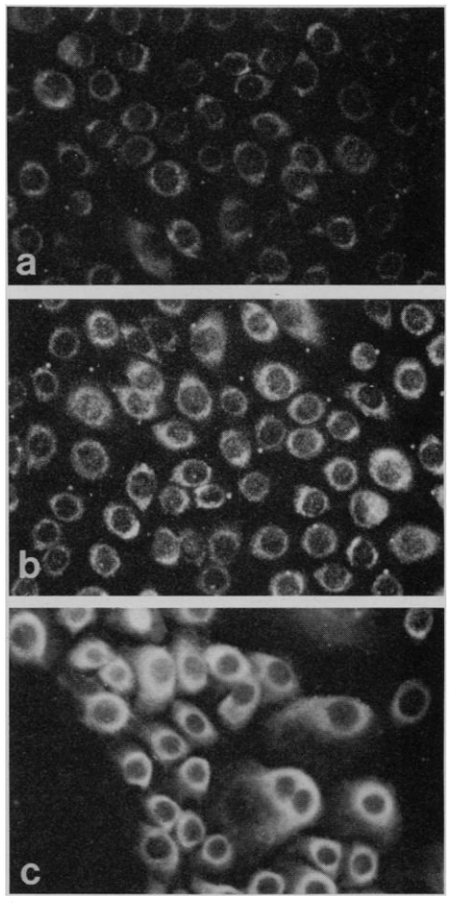
It's intriguing that keratins 5 and 14 have been implicated in the condition, notes Epstein, because they combine to form the keratin filament network in the immature keratinocytes at the innermost layers of the epidermis. He proposes that the mutations might impair keratin association and network assembly. This proposal is based partly on his group's finding that the keratin 14 mutation introduces a kink in a helical region of the protein that distorts its structure. "This is a very satisfying mutation," says Epstein. "First, it is highly linked with affected individuals; it arose in the same generation as the disease; and it altered the protein in a way that makes sense with regard to the disease."

The Fuchs lab has also found a relationship between K14 and EB simplex in humans. In the 20 September issue of *Cell*, they reported the identification of a different mutation in the K14 gene from two patients who spontaneously developed the disease. The mutation in one of the genes was also shown to disrupt keratin network formation, Fuchs says.

Taken together, the work from both labs has powerful implications for the pathology of EB, says dermatologist Eugene Bauer, an EB specialist at Stanford University Medical Center. "A lot of other ideas fall out of this work," he says. "The possibility arises that other forms of EB simplex may be related to mutations in other keratin genes."

The work of the two labs also helps answer the Fuchs team's original question about keratin's role: It seems to provide structural integrity to the cell. "By losing the integrity of the [keratin] network, the cells become vulnerable to any external stress and shear readily," says Coulombe. Fuchs and her colleagues are currently exploring whether the more extreme mutations in keratin correlate with increased cell fragility and disease severity in transgenic mice.





Holding on. *The diagram above indicates how anchoring fibrils, which contain collagen VII, attach the dermis to the epidermis. Immunofluorescence staining shows that keratinocytes treated with transforming growth factor beta make more collagen VII.*

While the studies of the defect underlying EB simplex are providing new information about the outermost layer of the skin, the new work on a second and more serious form of the disease, called dystrophic EB, is helping illuminate the structure and composition of the underlying layers, as well as the nature of the connections between the layers. In contrast to EB simplex, where the defect is in the epidermal cells, in dystrophic EB blisters form because the connections between the epidermis and the underlying dermis are weaker than they should be. As an external tissue, "the skin, is subject to friction," says dermatologist Robert Burgeson of Harvard Medical School. "If that interaction [between dermis and epidermis] is not stabilized, you're going to brush your skin off every time you brush against something."

Reasoning that dystrophic EB presents exactly the situation that Burgeson describes, Jouni Uitto and his colleagues at Thomas Jefferson University in Philadelphia decided that the gene for type VII collagen, a protein found by Burgeson to make up the anchoring fibrils that help connect the two skin layers, would be a good candidate for the site of the mutation that causes the disease. And in the October issue of the *American Journal of Human Genetics*, they report that a mutation in the gene is indeed closely linked to dystrophic EB. They found that all 20 affected individuals in four generations of a large Finnish family have the mutation, while none of the 22 unaffected individuals they studied have it.

Since most individuals who have dystrophic EB have less than the normal number of anchoring fibrils in their skin, Uitto proposes that the collagen VII mutation might disrupt the fibril assembly. Alternatively, it might prevent the collagen from being secreted from the cells that make it, or it might give rise to faulty attachment sites between the fibrils and the layer of connective tissue between the dermis and the epidermis. The exact defect in collagen is something Uitto and his colleagues are currently exploring. The work may also help explain why skin ages. "Skin in the elderly gets more fragile," Uitto says. "I am inclined to think that loss of anchoring fibrils contributes to that."

While researchers have not yet identified all of the mutations that can cause the various forms of EB, they are hopeful that the genes already identified will allow prenatal diagnosis in some affected families. What's more, they say, eventually gene therapy, where mutated keratin or collagen genes are replaced by healthy ones, may even be possible. "Although a cure may be a long time in coming, the skin may prove amenable to gene therapy because it's on the surface of the body and is easily accessible," says Fuchs.

And treatment for diseases involving collagen VII may require even less technical wizardry, says Uitto, whose group has evidence that collagen VII expression can be enhanced by transforming growth factor beta. Bauer, however, cautions that the factor is not likely to stimulate collagen VII expression specifically. But in a field that has recently seen such a rush of insight, it's reasonable to think that more epiphanies will soon follow. ■ MICHELLE HOFFMAN