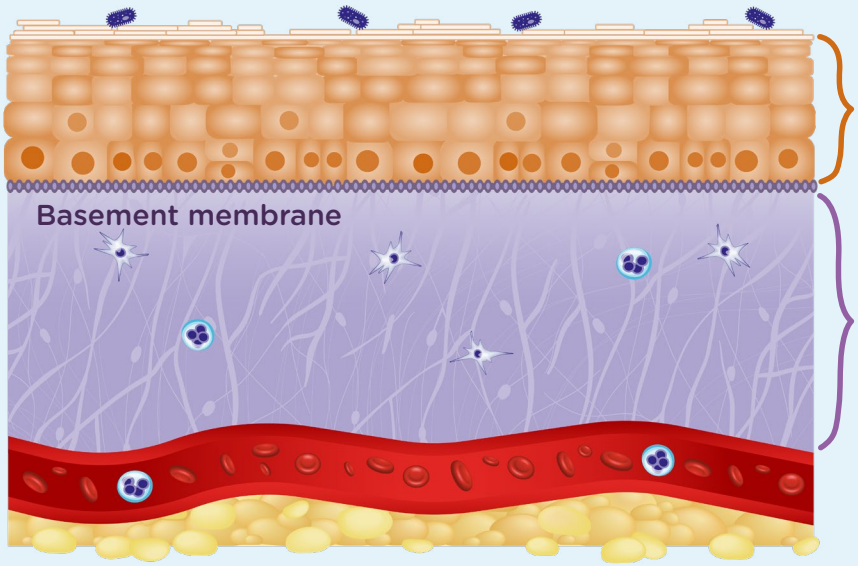
The science behind EB skin

What is skin?

Skin is the largest organ of the body. It is a flexible shield, protecting the inside of the body from the outside world. It is made from cells and proteins arranged in a very organised way to give strength, flexibility, sensation and waterproofing. Similar proteins and cells make the lining of the mouth and other openings into the body so epidermolysis bullosa (EB) symptoms can affect a person's insides as well as their skin.

Skin structure

Skin has an outer layer, called the epidermis (where blisters form in EBS), and a lower, thicker layer called the dermis (where blisters form in DEB). The epidermis and dermis are held together by a thin layer of protein called the basement membrane (affected in JEB). Exam answers naughtily written on the surface of the epidermis only last a few days, while tattoo ink, injected into the dermis lasts there forever. Bacteria live harmlessly (and helpfully) on the skin surface but can't get through it unless the skin is damaged.



The epidermis is the surface layer of skin (orange)

The dermis is the lower layer of skin (purple)

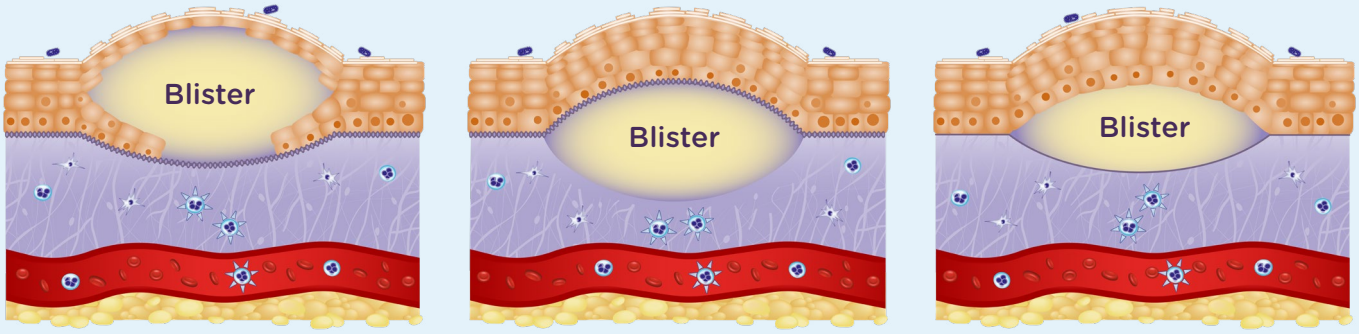
The epidermis is made of keratin protein and cells called keratinocytes, that make keratin. The epidermis can be as thin as paper or thicker than a credit card in different areas of the body. Keratinocytes near the basement membrane divide and the new cells push the older keratinocytes up towards the surface of the skin. Keratinocytes live for a few weeks and make more and more keratin until they are full of it, become very flat (squamous) and die. This creates a waterproof layer of dead cells and keratin at the skin surface that naturally flakes away to be replaced from cells beneath. Keratin protein is made from different keratin subunits, joined and twisted together in long chains, each one encoded by its own gene. Changes in the genes for keratin-5 and keratin-14 can cause the most common form of EB, EB simplex (EBS), where blisters form in the epidermis.

Beneath the epidermis is a thicker layer, called the dermis, containing blood vessels, nerves, hair follicles, immune cells and sweat glands. It varies in thickness from 0.5-4mm in different parts of the body. This layer is made mostly out of collagen protein and contains fibroblast cells that produce collagen, and immune cells that protect against germs. Like keratin, collagen is made from protein subunits, each encoded by a different gene, and twisted into fibres. Changes to a gene for collagen-7 can cause dystrophic EB (DEB).
Other proteins that can be missing or broken in EB include laminin, which is important in the basement membrane, and integrin which fixes cells into position in the skin. Changes to genes for laminin-5, collagen-17 and integrin can cause junctional EB (JEB). The rarest form of EB, Kindler EB (KEB), is caused by changes to the gene for Kindlin-1 which is another protein that helps skin cells to stick together.

Blisters

Skin is flexible, so it can stretch and contract over bones and muscles as they move under the skin. It also gets dragged and pulled when walking or gripping which rely on friction between the skin and another surface. When the key proteins that make the skin strong, are missing or not working properly, these pressures can cause the structure of the skin to pull apart. Liquid from blood vessels flows into the space created and a blister forms. Often red blood cells are left behind and the fluid appears clear or slightly yellow, but sometimes whole blood fills the gap and creates a blood blister that looks red. EB blisters can keep growing when the skin at the edges is pulled apart as the fluid stretches the blister. Underneath the blister, the broken skin is sore and vulnerable to infection by bacteria or other germs.

In different types of EB, the blisters can be in the epidermis (EBS), dermis (DEB) or at the junction of the two (JEB).

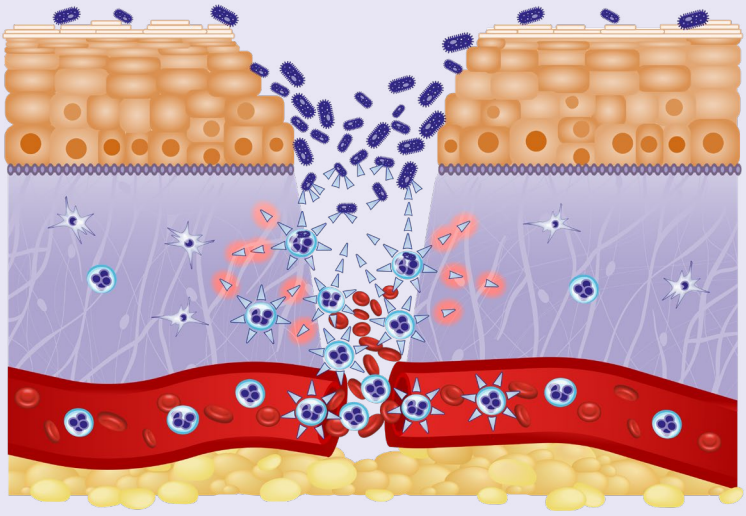


EBS Blister | DEB Blister | JEB Blister

Infections

Skin damage means that the barrier protecting the warm, wet, nourishing inside of the body is breached. Bacteria that can't penetrate healthy skin can get into a wound and multiply creating an infection that slows down healing and causes more damage. Antibiotics are medicines that stop bacteria from multiplying. They can slow down infections and give the immune system a chance to clear away the bacteria.

Damage to skin causes inflammation



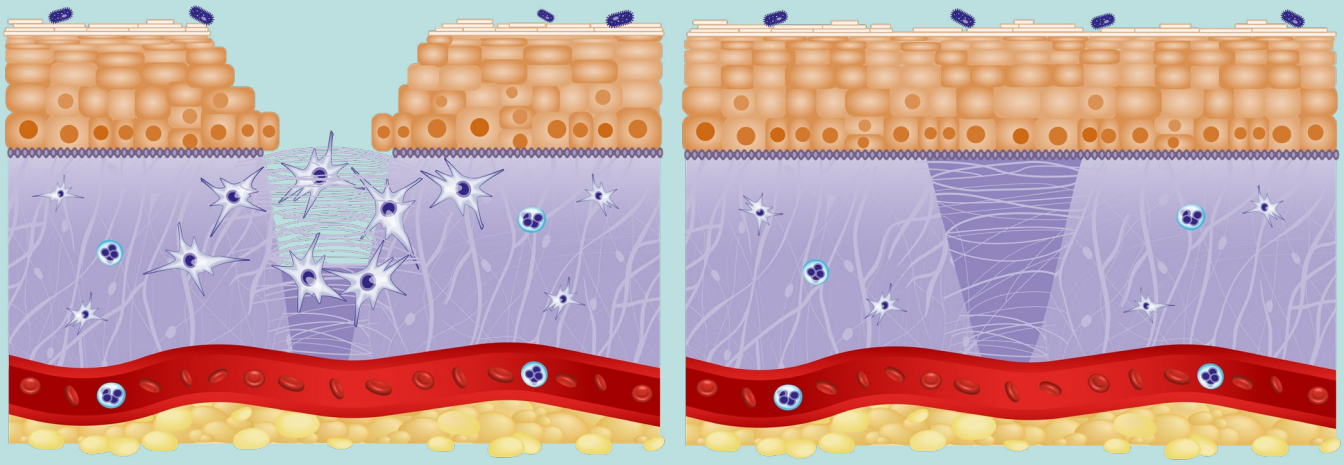
Inflammation is the name for the process of immune system cells and proteins reacting to skin damage. It can cause swelling, pain, warmth, itching, rashes and redness (on paler skin) as blood vessels expand to bring immune cells to the wounded area. The colour of blood comes from the red blood cells that carry oxygen to every cell. It also contains bigger white blood cells that are a key part of our immune system. Similar immune cells live in the skin and respond to damage by releasing proteins that encourage more immune cells to gather and behave in an aggressive way. They destroy and remove dead and damaged cells or cells infected with bacteria or viruses by releasing substances that kill cells, and proteins called antibodies that stick to bacteria and target them for destruction. Some immune cells kill bacteria by engulfing and destroying them. This process of inflammation produces symptoms like swelling, rashes and itching and can damage healthy cells.

Inflammation causes damage to skin

Inflammation is like police officers (white blood cells) responding to a riot. They stop circulating peacefully round the streets (blood) or chatting on street corners (skin) and call each other for back up. They put on their riot gear (activation), head for the damaged area and attempt to subdue anyone who looks suspicious (bacteria and dead, damaged or infected cells). Inflammation is an important process but can be quite harmful to the surrounding area and shouldn't go on for any longer than it needs to. Some immune cells act to tell the others to "calm down!" when the inflammation is no longer needed.

Healing skin after wounding

If only the top layer (epidermis) of skin has been damaged, it can often heal so well that it looks like there has never been an injury. Some types of EB (simplex) are more likely to lead to scarless healing than others (dystrophic and junctional). Repairing a deeper wound uses a process called fibrosis and produces a scar.

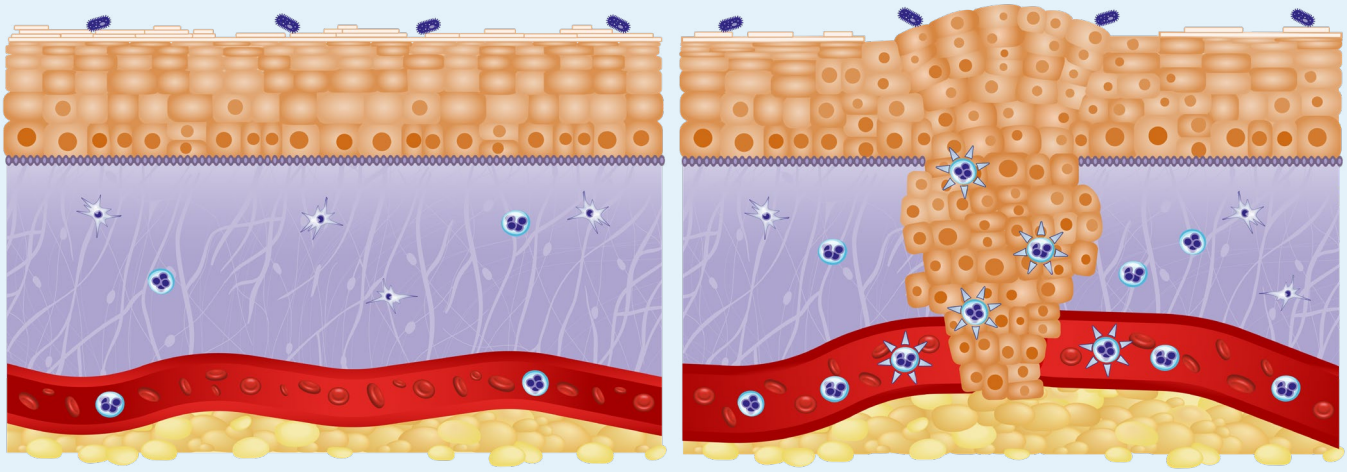


Fibrosis involves cells called fibroblasts, that exist throughout the dermis, becoming more active when the skin needs to be repaired. Fibroblasts can change into myofibroblasts that contract to pull a wound closed and make sticky proteins like collagen to glue our skin back together.

Scarring can't perfectly replicate the skin that was there before and can cause symptoms such as narrowing of a person's mouth, windpipe or food pipe, or fusion of fingers and toes. Scars can be less stretchy than the original skin and look different in colour and texture.

Skin cancer

The risk of skin cancer is increased in some types of EB. Cancer happens when DNA in one cell is damaged and instructs it to stay alive and keep dividing instead of dying when it should. The new cells made when it divides carry the same, wrong instructions to stay alive and divide again. Cancers don't grow new functioning organs: lung cancer doesn't grow a new lung and skin cancer doesn't grow new skin. It is just one type of cell that is multiplying when it shouldn't and creating a lump or bump. These lumps of cancer cells can divert blood vessels to bring them extra oxygen and nutrients so they can continue growing and dividing. A cancer can bleed, squash nerves and do damage by interfering with normal cells. If a cancer cell breaks off the lump, it can be carried around the body, stick somewhere else and carry on multiplying as a 'secondary' cancer (metastasis).



The immune system can respond with inflammation to bring white blood cells to an area where cancer is doing damage, but they may not be able to tell the difference between a person's own healthy cells and the ones that are part of a cancer. Inflammation is important for our bodies to react to a wound, but long-term inflammation can support the development of cancer.

Skin research

EB research tries to find ways to reduce the initial skin damage, calm down inflammation, fight pain and infection, control scarring, and prevent cancer developing to make the symptoms of EB easier to live with, as well as looking for ways to fix the original genetic changes responsible for missing or broken skin proteins.

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