Geistlich
Biomaterials

MIRACLES OF REGENERATION

... and how collagen expertise led to a new product

The wonderwork of regeneration

Deer are the only mammals capable of regenerating a body part. Once a year, they grow new antlers – a genuine regeneration feat. Scientists have long studied how new antler bone is formed. It is thought that stem cells play a significant role in this process. Stem cells are present in the pedicle periosteum, where they are periodically active and produce new antler bone each year.

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Biomaterials

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Is collagen a miracle substance? Exactly.

In "Miracles of Regeneration" we invite you to immerse yourself in our world, and share our deep fascination with the big and small wonders of regeneration.

You will learn which representatives of the animal kingdom are true masters of regeneration, and how nature teaches us the key to regeneration: collagen. We introduce you to this miracle substance and investigate how cells interact with this protein.

We also talk to the scientists behind the achievements of Geistlich Pharma. About their motivation and their drive to generate progress through innovation. In two interviews we look behind the scenes and glimpse the secrets behind a new product of Geistlich Pharma.

I am personally delighted to present you with this printed piece of our inspiring cosmos. I am convinced that this will make our passion for the subject more tangible.

Get to know us. Relax and regenerate with our reading.

Paul Note
CEO Geistlich Pharma

Paul Note in the Geistlich Pharma development laboratory in Wolhusen, Switzerland.

A new approach regeneration

Soft tissue regeneration using subepithelial tissue grafts has many disadvantages. But Geistlich Pharma now offers an alternative.

When a tooth needs to be replaced by a dental implant, sufficient bone must be available.[1,2] For this, the soft tissue at the implant site also plays a major role: On the one hand, it may be necessary to augment the gingival tissue surrounding the implant to make the contours of the gum tissue and the emergence profile of the implant esthetically more pleasing.[3,4] On the other hand, sufficiently thick soft tissue provides long-term protection against loss of the underlying bone.[5]

To date, subepithelial connective tissue is considered the gold standard for the augmentation of soft tissue.[6,7] Dentists take such grafts from patients' palates and transfer them to the extraction or implantation site, or to the surface of exposed dental roots.

But this method has a number of drawbacks. Depending on the anatomy of the palate, grafts differ in height, thickness and length.[8] Anatomical factors such as nerves and blood vessels in the palate restrict the dimensions of the grafts.[9–11] Last but not least, graft tissue harvesting results in a second wound at the removal site, causing bleeding, pain, swelling, and occasionally also numbness or infections.[12–15]

However, Geistlich Pharma offers an alternative to autologous connective tissue grafts. It does not depend on the anatomy of the palate, the risk of developing complications is lower, and the procedure is less painful for patients.[16] This alternative is a collagen matrix that can augment soft tissue just as effective and long-lasting as autologous connective tissue.[16–18] A breakthrough in soft tissue regeneration.

A reference list can be found at the end of this brochure.

to soft tissue

> **All patients ask for minimally invasive procedures. Time and again, patients tell me they do not want tissue to be taken from the palate.**

Dr. Karin Jepsen, Germany
Center for Dental and Oral Medicine, Dept. of Periodontology, Operative and Preventive Dentistry

Dr. Karin Jepsen, a senior dentist, with a patient.

Inspiration from nature

Join us on a journey through the animal kingdom to discover the secrets behind the animals' regenerative properties.

Some animals have amazing regenerative abilities. Sharks, for example, often lose one or several teeth while hunting prey, but are able to regenerate them without difficulty. More bewildering still is the regenerative ability of a salamander called axolotl, which is able to regrow a complete leg. As for hydras, they actually seem immortal.

Forever young

Hydras, a type of freshwater polyp, have spectacular abilities: cut into pieces, these animals are able to regenerate whole polyps from tiny bits of their bodies. This is made possible by stem cells which keep their ability to divide and to develop into all types of cells needed for the regeneration of a whole organism or single body parts. However, despite this amazing regenerative ability, polyps too are not immortal. Although a hydra does not age and its mortality risk remains the same over years, individuals do succumb to a natural death.

Teeth reloaded

A shark's dentition is unique: new teeth develop throughout the animal's life, on the inner surface of its jaws. Accordingly, every shark's dentition contains teeth in various developmental states. The bull shark, for instance, has up to seven rows of teeth. When one of the front teeth is lost, another one in a back row slowly straightens up and replaces its predecessor. This ability is an absolute necessity for sharks. When they hunt seals and fish, numerous teeth are damaged or lost. It is therefore quite normal that a shark develops up to 30,000 teeth during its lifetime.

Limbs and organs regrown

Salamanders and newts, such as the axolotl, have the ability to regenerate legs, arms, parts of the central nervous system, and even heart tissue. When an axolotl's heart needs repairing, previously specialized cells regress to become undifferentiated cells and then develop into heart muscle cells. During this regeneration phase, the axolotl reduces its blood pressure and its metabolism, so as to channel as much energy as possible into the healing process. After approximately two weeks, the newt's heart will again beat as if nothing had ever happened.

How do these animals do this? There is no simple answer to this question, as different regeneration mechanisms exist. But one of the secrets lies in the regenerative power of stem cells. These cells have not yet taken on a specific form or function, and are able to develop into all sorts of cell types. They can for instance become bone, brain or connective tissue cells. What mechanism regulates this differentiation?

Collagen can play a role in this process. In the human body, collagen provides some sort of external skeleton to cells. In so doing, collagen also determines how yielding or rigid the environment of the cell is. Fibroblasts take their bearings from collagen structures when they infiltrate a tissue for regeneration purposes, following a skin injury, for example.[19] For this purpose, cells make use of their cytoskeleton to test the rigidity of their environment.[20,21]

These findings are the basis of the Geistlich scientists' efforts to naturally renew soft tissue. Their idea was to build an environment in which fibroblasts create new connective tissue of their own accord. Thus, the regeneration concept was born: a collagen matrix!

A Miracle Substance

Collagen is the basic component of Geistlich's collagen membranes and matrices. But this miracle substance is also indispensable in humans. Without it, the human body would be a structureless heap of tissue.

Without collagen, the human body would be a structureless heap of tissue. Collagen is he most prevalent protein in the human body. Almost 30 percent of our proteins are collagen, and our body contains 30 different types of it. An important feature of collagen molecules: they do not like to be alone. They intertwine, cross-link and connect to form fibrils and fibers. If all the collagen molecules in the human body were to be unfolded and strung together, the strand would stretch from the earth to the moon 10,000 times.

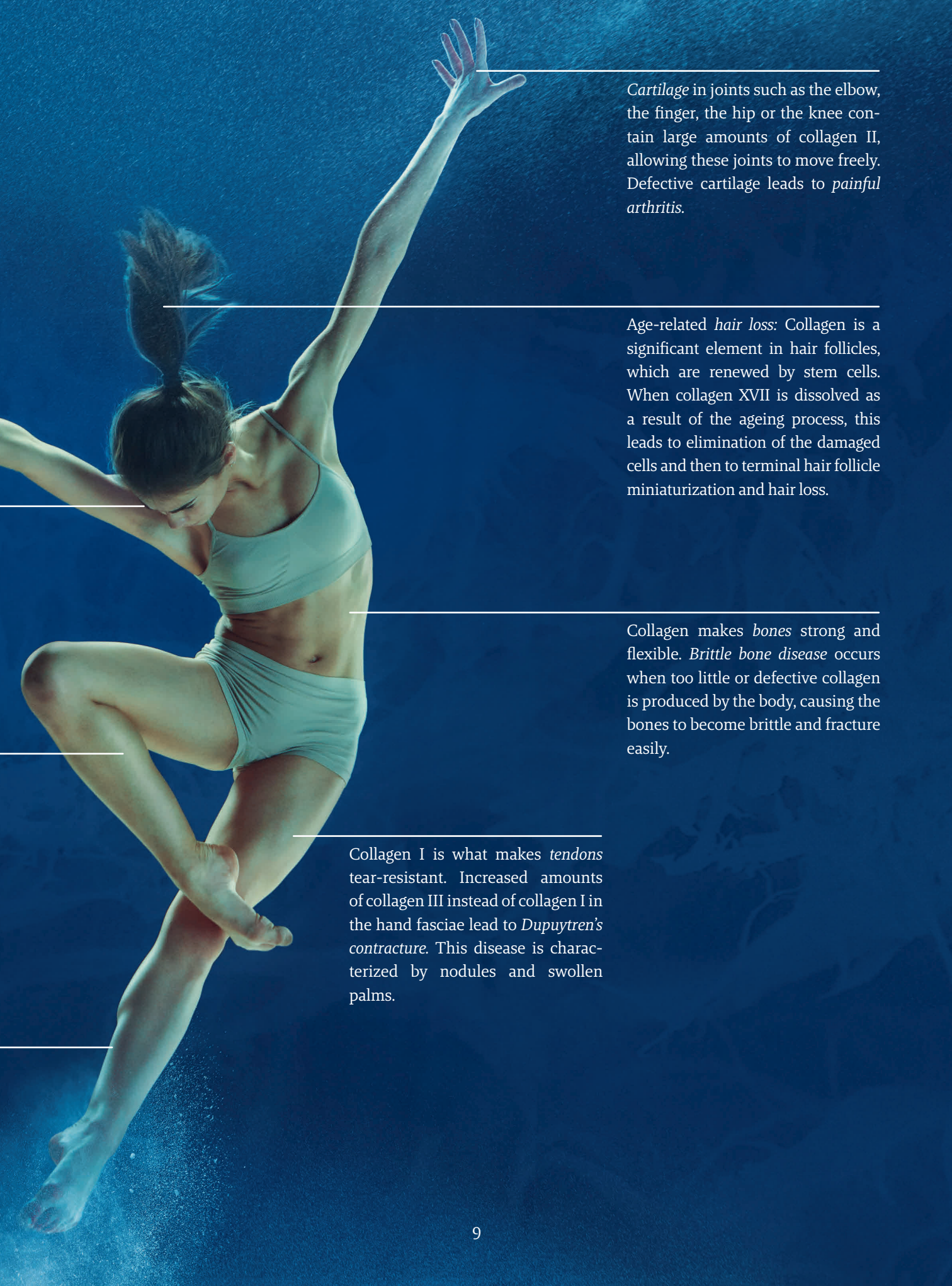
Why do we have so much collagen? Because we need it in most parts of our body, for example in our bones. Without collagen, our skeleton would be very brittle. This miracle protein is what gives it stability. Collagen molecules can also absorb enormous traction forces. A tendon, consisting of nearly pure collagen, can endure a traction force of 500 to 1,000 kilograms per square centimeter.

Collagen is vital not only for tendons and the body's skeleton, but also for what is called the extracellular matrix, the skeleton surrounding each and every cell. For instance, this matrix gives connective tissue cells, the fibroblasts, their shape. Additionally, collagen provides a kind of construction plan that allows single cells to connect and form a tissue.[22] With collagen's many functions, one thing is certain: Malfunctions of these proteins often lead to serious diseases.

Teeth are well anchored to the bone owing to *periodontal ligaments* which also consist of collagen fibers that are rapidly converted and renewed. Collagen renewal requires vitamin C. *Vitamin C deficiency* leads to scurvy and can result in teeth loss.

Skin consists mainly of collagen I and III. Collagen VII is only present in small amounts, but due to defects in collagen VII the different skin layers epidermis and dermis do not adhere to one another. As a consequence, the skin blisters and peels off – a desease called *epidermolysis bullosa dystrophica.*

Ligaments connect bones and stabilize joints. They consist mainly of collagen I. As collagen is not very elastic, ligaments can easily be *sprained* or even torn.

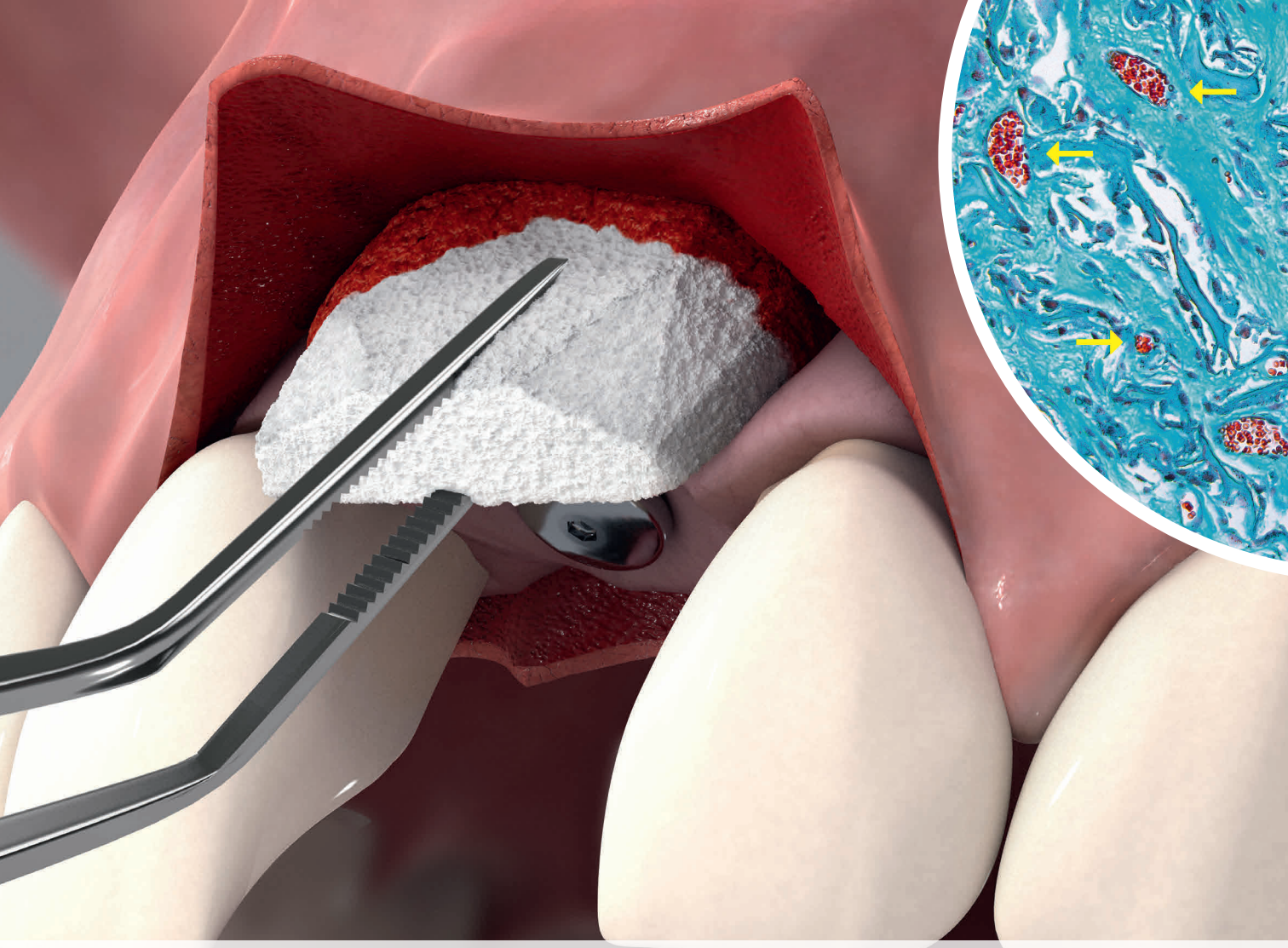


Cartilage in joints such as the elbow, the finger, the hip or the knee contain large amounts of collagen II, allowing these joints to move freely. Defective cartilage leads to *painful arthritis.*

Age-related *hair loss:* Collagen is a significant element in hair follicles, which are renewed by stem cells. When collagen XVII is dissolved as a result of the ageing process, this leads to elimination of the damaged cells and then to terminal hair follicle miniaturization and hair loss.

Collagen makes *bones* strong and flexible. *Brittle bone disease* occurs when too little or defective collagen is produced by the body, causing the bones to become brittle and fracture easily.

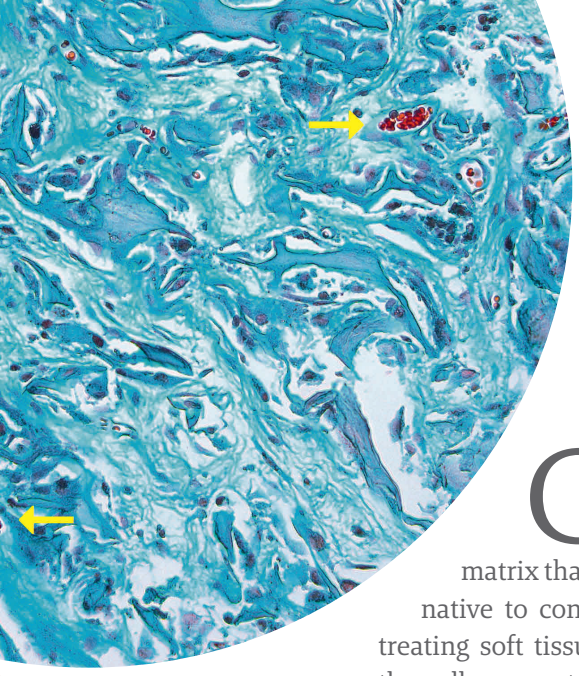
Collagen I is what makes *tendons* tear-resistant. Increased amounts of collagen III instead of collagen I in the hand fasciae lead to *Dupuytren's contracture.* This disease is characterized by nodules and swollen palms.



As shown in the picture, dentists can insert Geistlich Fibro-Gide® using the minimally invasive pouch technique. For this purpose, the matrix is first cut to shape in a dry or moist state. Geistlich Fibro-Gide® increases in volume and exhibits adhesive properties when moistened with blood. Tension-free wound closure is key for treatment success.

One product
TWO properties of collagen combined

In nature, tissue regeneration requires a suitable environment as well as an "assembly manual". Also the new collagen matrix Geistlich Fibro-Gide® acts in dual way to effect tissue augmentation.



Geistlich Fibro-Gide® supports angiogenesis, formation of new connective tissue and stability of the collagen network in submerged healing situations.[16,33] The histology shows the formation of blood vessels in the collagen matrix 2 weeks after implantation (yellow arrows).

Geistlich Fibro-Gide® is a resorbable volume-stable collagen matrix that can be used as an alternative to connective tissue grafts for treating soft tissue deficiencies.[6,7,16] Once the collagen matrix is in place, cells from the surrounding tissue colonize it and use it as a scaffold to form new connective tissue. Over time, Geistlich Fibro-Gide® integrates completely, leaving behind regenerated soft tissue.[23]

Pore size is crucial for cell migration

To allow for rapid colonization of Geistlich Fibro-Gide® by fibroblasts, the pores of the collagen matrix must display an appropriate diameter.[24,25] Geistlich Fibro-Gide® features optimal pore sizes of 65 µm that allows cell migration, tissue regeneration and vascularization.[26–32] This means, Geistlich Fibro-Gide® consists of 93 percent of pores that provide an environment for the infiltration of patients' blood and tissue to integrate into the matrix.[26–32]

Geistlich Fibro-Gide® is as compressible as a sponge

Due to its highly porous structure, Geistlich Fibro-Gide® acts like a sponge which ensures a good nutrient delivery in a few days[26] and allows resistance against movement forces caused by speaking, swallowing, the lips and tongue. In comparison with competing products, the new collagen matrix is much more compressible, yet returns to its original volume after having been subjected to compression.[34]

Smart cross-linking makes it possible

Geistlich's goal was to fulfill the need of many dentists to have a collagen matrix that is as effective as a connective tissue graft in gaining soft tissue thickness. Therefore, the R&D department of Geistlich developed a smart collagen cross-linking process that balances mechanical volume stability with biocompatibility and tissue integration in the human body.[26]

Cross-linking occurs naturally in collagen. But in order to provide a volume-stable collagen matrix, the developers added further smart cross-links to the collagen of Geistlich Fibro-Gide®. Finding the optimal level of cross-linking was essential: A high degree of cross-linking increases the risk of impaired biocompatibility and tissue integration and can cause dehiscences, graft exposures and delayed wound healing.[35] With Geistlich Fibro-Gide®, Geistlich can now offers a smart cross-linked collagen matrix with excellent biocompatibility and healing properties which was also confirmed by extensive pre-clinical and clinical testing.[33,36]

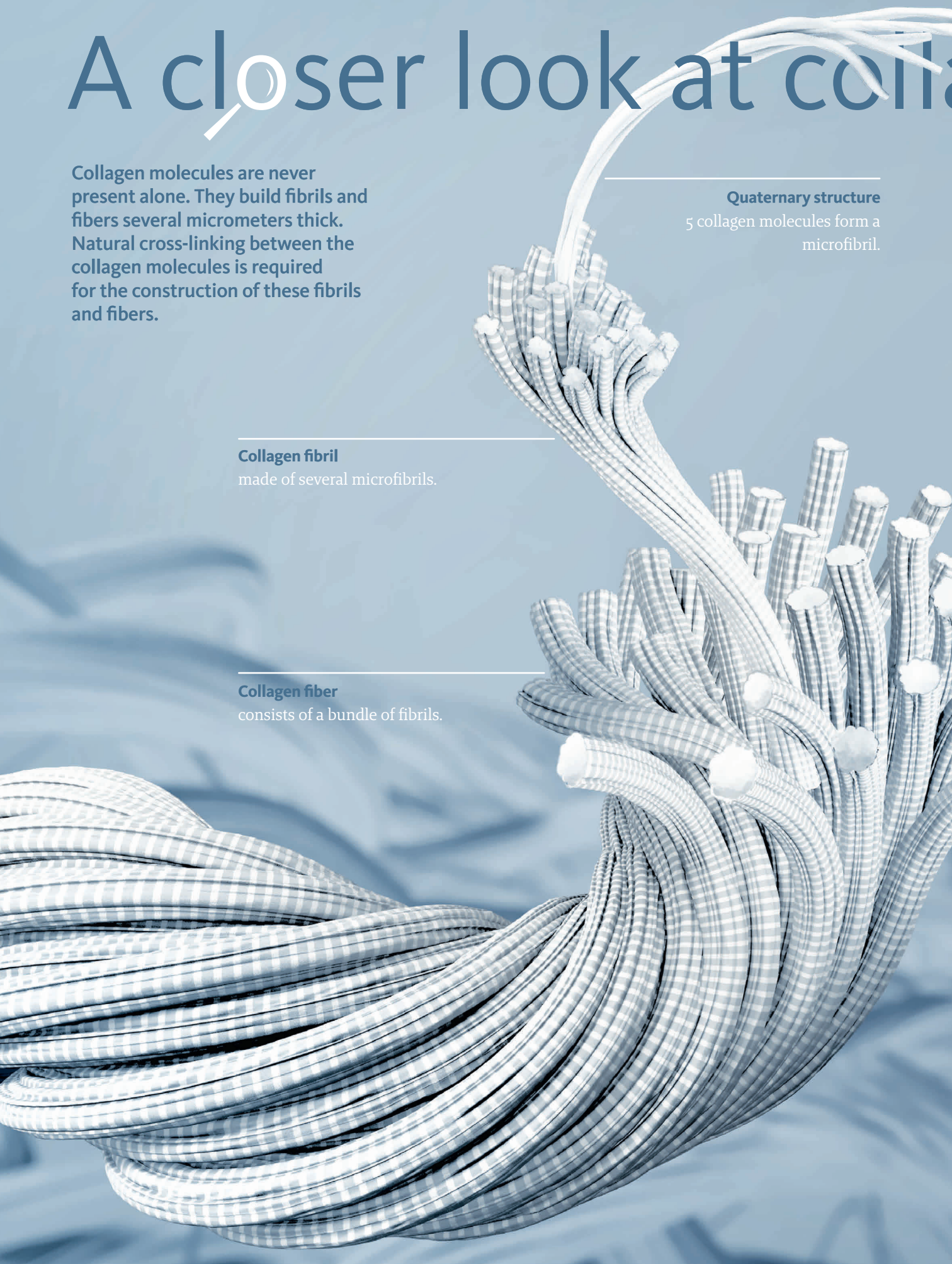
A closer look at colla

Collagen molecules are never present alone. They build fibrils and fibers several micrometers thick. Natural cross-linking between the collagen molecules is required for the construction of these fibrils and fibers.

Quaternary structure
5 collagen molecules form a microfibril.

Collagen fibril
made of several microfibrils.

Collagen fiber
consists of a bundle of fibrils.



agen

Tertiary structure
Each collagen molecule consists of 3 alpha-helices.

Secondary structure
A polypeptide chain of amino acids forms an alpha-helix.

Animal implants in the human body

It is another fascinating property of collagen that makes it possible to implant a graft of animal origin into the human body without difficulty. Within the evolutionary context, collagen is a very old protein. It is already present in phylogenetically very ancient living beings such as hydras, jellyfish and sponges. As collagen is vital in all animals, it has hardly changed in the course of evolution, meaning that the collagen in pigs is very similar to the one found in humans. This is why Geistlich Fibro-Gide® made from animal source material is well tolerated by patients.[23]

thousand

New Geistlich Pharma filling system in Wolhusen, Switzerland.

“We went through more than one prototypes”

The journey from the idea for a volume-stable collagen matrix to the final product that fulfills the market needs was a long one. Dr. Mark Spilker, Chief Scientific Officer (CSO) at Geistlich Pharma, tells the story of the development of Geistlich Fibro-Gide®.

> The clinical testing at Geistlich Pharma is extensive: it even exceeds regulations.
>
> *Dr. Mark Spilker, CSO at Geistlich Pharma*

How does a product like Geistlich Fibro-Gide® come to life? Where does it all start?
It always begins with a need. That is the driving force. And in dentistry, there is a real necessity to generate soft tissue volume, be it around the site of an implant or to treat receding gums.

Geistlich Fibro-Gide® is chemically cross-linked. Is this a big deal?
It needs specific expertise to create a cross-linked product that works really well. If the cross-linking is done in the wrong way, the product might get resorbed too slowly or cause an inflammatory response.

What motivated Geistlich Pharma to use cross-linking nonetheless?
Because cross-linking was exactly what we needed to create a volume-stable collagen matrix. But it was a very long, iterative process to come up with the final product. The investigators had three variables that they could modify: the matrix, the cross-linking method and the degree of cross-linking. By studying variations of these three factors, they went through more than 1,000 product configurations. Eventually, they narrowed it down to a handful of prototypes.

How were these prototypes evaluated?
They were tested in pre-clinical studies with animals and in clinical studies with

Dr. Mark Spilker at Geistlich Pharma headquarters in Root, Switzerland.

In a Nutshell

Made of Collagen

Geistlich Fibro-Gide® is a porcine, porous, resorbable and volume-stable collagen matrix.[42]

Volume Stability

The reconstituted collagen undergoes smart cross-linking for volume stability of the device.[42]

Soft-Tissue Formation

In vivo animal models have shown good integration of Geistlich Fibro-Gide® into the surrounding soft-tissue while maintaining stability.[36]

Supports Soft-Tissue Integration

The porous network of Geistlich Fibro-Gide® supports angiogenesis, formation of new connective tissue and stability of the collagen network in submerged healing situations.[33,38]

actual patients. And the clinical testing at Geistlich Pharma is extensive: it even exceeds regulations. The EU, for example, requires only one clinical study. But Geistlich Pharma carried out multiple clinical studies.

What was the outcome of the clinical studies?

I was really surprised when I saw the results from clinical studies, showing that Geistlich Fibro-Gide® is as effective as connective tissue grafts in the augmentation of soft tissues. Since the benefits of Geistlich Fibro-Gide® over a tissue graft are self-evident (no need for a second surgical site, shorter surgery time, less pain perception) the results were enough to take the product to the pre-launch phase.

What happens during the pre-launch phase?

The pre-launch phase is not required by law, but it is done because Geistlich Pharma is an evidence-based company. Just because our product works in the clinic does not mean it works in practice. We want to know how the product performs in practice in different countries, with different practitioners, patients and surgical techniques. That is why we send the product out to a selected group of dentists, so called pioneers, who test the product and give us feedback.

What kind of feedback do these dentists give?

For example, they can give us feedback on how the product performs with thick or thin alveolar biotypes. Or how our products need to be trimmed to shape for different applications, such as for esthetic use or around implants. This feedback also influences the technical product guide for dentists. And once this process has been completed, the product enters the launch phase, during which it is marketed and sold.

Before the product launch

Before a new product is launched on the broad market, selected dentists gain clinical experience with the new product.

The clinical experts involved in Geistlich's pre-launch phase test a new product for different indications and exchange information with each other and Geistlich: Which techniques work particularly well? What are the pitfalls? What was the learning curve? What to recommend to someone just starting to use the product?

Before launch, a pre-launch phase took place in seven European countries. One of the pioneers in Italy was Prof. Leonardo Trombelli, Ferrara, who shares his experiences using Geistlich Fibro-Gide® with other dental practitioners in the picture.

> **During the pre-launch phase, we drafted recommendations for the handling of the product. Now we organize workshops to share our knowledge with our colleagues.**
>
> *Prof. Leonardo Trombelli, University of Ferrara, Italy*

Prof. Trombelli at a workshop in Italy.

1851

The success story of Geistlich Pharma begins in 1851. The family business refines bones and tissue and processes these to make glue. Heinrich Geistlich founds Switzerland's first glue factory in a street now called "Leimgasse" ("Glue Lane"). The residents complain about the foul odor emanating from the bone boilery, forcing the company to move to Schlieren.

The Geistlich household glue produced in the early days is still in the memory of many Swiss citizens who used it in school or at home.

1939

Geistlich's commitment during World War II to produce a food supplement marks its entry into the pharmaceutical industry. Later the company expands its product range to include Decalcit for calcium and vitamin D deficiencies.

1899

In 1899, the entrepreneurial pioneer Eduard Geistlich Sr. takes over a factory in Wolhusen to produce additional animal-based glues and bone fertilizer. During World War II, Geistlich is commissioned by the Swiss Confederation to develop food supplements to fight war-induced deficiency symptoms.

Geistlich: A collagen love-story

Originally a glue-producing company, Geistlich entered the pharmaceutical industry during the Second World War. Its expertise regarding bone, tissue and collagen allowed the company to become a leader in regenerative medicine today.

2018

Today, Geistlich Pharma is a leading supplier of regenerative biomaterials. For decades, the company, employing approximately 500 people around the world, has been a worldwide market leader in the area of regenerative dental medicine.

2017

1996

Ten years later the company made another breakthrough, thanks to its collagen expertise: Geistlich Bio-Gide® was the first collagen-based resorbable membrane used for oral tissue regeneration. It soon established itself against traditional, synthetic membranes.

2014

Taking its experience with regenerative biomaterials further, Geistlich developed Geistlich Mucograft® – a unique collagen matrix designed specifically for soft-tissue regeneration. The matrix eliminates the need for painful graft harvesting during soft-tissue regeneration.

1986

Eduard Geistlich's son Peter took the company into the field of regenerative medicine, drawing on its experience using bone materials: Geistlich developed the natural bone replacement material Geistlich Bio-Oss®. Launched in 1996 it is now used every 18 seconds in the world.

Senior dentist PD Dr. Daniel Thoma at his surgery.

Is a scientific network an asset? Exactly.

PD Dr. Daniel Thoma has been involved in the development of Geistlich Fibro-Gide® from the beginning and conducted several pre-clinical and clinical studies with the product. He is convinced by the results.

> **As a clinician and researcher I believe that Geistlich Fibro-Gide® is a breakthrough in soft tissue regeneration.**
>
> *PD Dr. Daniel Thoma, Center of Dental Medicine of the University of Zurich, Switzerland*

The development of Geistlich Bio-Oss® marked the company's entry into the field of regenerative medicine. But it was also the beginning of extensive collaborations between Geistlich and academic institutions. Drawing on its scientific network, the company performs clinical and pre-clinical studies to test its products. This was also the case during the development of Geistlich Fibro-Gide®.

PD Dr. Daniel Thoma is one of the clinical experts who accompanied the development of Geistlich Fibro-Gide®. This senior dentist at the Center of Dental Medicine of the University of Zurich says that even though connective tissue grafts represent the gold standard in terms of soft tissue regeneration, research shows that the results with Geistlich Fibro-Gide® are just as satisfactory. This is why Dr. Thoma tells his patients that although less research has been conducted on Geistlich Fibro-Gide® than on connective tissue grafts, he recommends the collagen matrix as an alternative. "In this way, my patients benefit from a shorter treatment period, they experience less swelling and, above all, this procedure requires surgery in only one spot."

Convincing results from literature

The collagen matrix was investigated in preclinical and clinical studies. Comparison with the gold standard yielded convincing results.

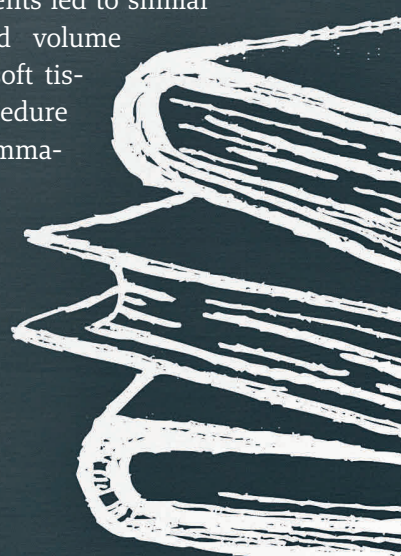
A collagen matrix is as good as a connective tissue graft

Soft tissue augmentation using a volume-stable collagen matrix is as effective as that achieved through connective tissue grafting[16,17] and remains stable for more than one year.[18] This was discovered in the context of a randomized, controlled clinical study in which 20 patients with insufficient soft tissue volume at implant site were enrolled and treated with either a collagen matrix or a connective tissue graft. The volume of the soft tissue was monitored up to 1-year follow-up after final reconstruction by taking jaw imprints and tissue samples before and after surgery. Results demonstrated no significant difference in terms of quality and quantity of the augmented soft tissue over the whole observation period.[17,18] In addition, the volume-stable collagen matrix guarantees shorter surgery time, lower pain perception and does not require a second surgical site.

Soft tissue volume augmentation in a dog mandible

The Geistlich product also performed well in pre-clinical studies aimed at investigating the reaction of the canine alveolar ridge to the volume-stable collagen matrix.[23] For this purpose, ninety days after teeth extraction the volume-stable matrix was inserted and tissue probes were taken at six different time points up to 90 days. Findings demonstrated that the collagen matrix had been almost completely resorbed and replaced by connective tissue fibers.[23]

In another pre-clinical study, three weeks after implant placement, either a collagen matrix or a connective tissue graft were used at implant site. After one, four and six months, imprints from all mandibles[37] and histological examination[38] demonstrated that both treatments led to similar enlargement and volume increase of the soft tissue. Neither procedure triggered inflammatory reactions.



“Research entertains my brain”

Biomedical engineer Niklaus Stiefel has been working with Geistlich Pharma since 2006. He is the head of Material Research Biochemistry.

Niklaus Stiefel in the Geistlich Pharma development laboratory in Wolhusen, Switzerland.

Niklaus Stiefel, in your time working with Geistlich, what has changed in the general understanding of collagen?

When I started working here, it was believed that cells attach to collagen. We mainly thought of collagen as a scaffold that does not interfere with cells. Today we know that the mechanical properties of a collagen scaffold play a role in the differentiation of stem cells.[39–41] Collagen is still predominantly a scaffold providing anchorage points. But now we know that it has an additional biological function.

How does the scaffold influence cell development?

Cells probe the stiffness of a material by means of their cytoskeleton.[20,21] This triggers a downstream cascade that determines how these cells differentiate.

Did you never want to do basic research and find out important things?

That is a good question. The ego of course is an important thing. But in the end, what are you working for? Are you devoting your time to be famous, or is it to help patients?

Do you know the whole secret behind Geistlich Fibro-Gide®?

We did all the analytics on it. We know very well how the matrix works and how it compares to existing products.

The product is on the market now. What more can be discovered?

Geistlich aims to be THE regeneration company in 2030. We currently explore and invent new products in the dental and orthopedic field.

But you personally, what secret would you like to reveal?

The promise of biomaterials is in the end immortality. An old dream of humanity. To achieve this old human dream, many scientific questions have to be solved. Today we treat bone, skin and cartilage on a regular basis. However, in a long term perspective we aim to regenerate complex organs: heart, liver, kidney.

How old do you want to become?

As long as I am happy with my life, I could probably live forever.

What makes you happy?

Interesting work, where you can discover new things and work for the benefit of others – one could call it brain entertainment. And of course a social life and sport.

Picture credits

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The matrix through the microscope

The pores of the collagen matrix Geistlich Fibro-Gide® are visible in this image from an electron microscope.

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