

9 Medical knowledge from the sea



> Marine organisms such as bacteria, corals and sea sponges contain thousands of interesting substances that could provide us with the medications of the future. Some of these agents have already been approved as drugs. Research on primordial organisms can reveal both how diseases occur and how they can be treated. Before the treasure trove beneath the sea can be claimed, however, some legal issues must be resolved.



Active substances from marine creatures

> Substances from the sea are already used as cancer drugs and painkillers, while other preparations are undergoing trials. But searching for new substances is a time-consuming business. Genetic analysis could speed up the process.

Source of healing since ancient times



9.1 > Works by the ancient Greek dramatist Euripides (ca. 480 to 406 B.C.) are still being staged today. The sea is a fateful element of his tragedies, acting as both a threat and a source of life.

For thousands of years people have believed in the healing power of the sea. As the Greek dramatist Euripides says in one of his plays about Iphigenia, “The sea washes away the stains and wounds of the world”. The ancient Egyptians and Greeks examined the effects of seawater on human health. They credited the sea and the substances it contained with healing properties. Marine products have for centuries been an integral part of folk medicine all around the world. For example, sea salt has traditionally been used to treat skin diseases, and algae to treat parasitic worms.

In 1867 the French doctor La Bonnardière introduced the classical thalassotherapy (seawater therapy) and climatotherapy to Europe, reinforcing people’s belief in the therapeutic properties of the sea. However, mythologizing these powers has also brought forth irrational fruit – the notion that eating turtle eggs or shark fins increases virility, for instance. Unscrupulous businesses have exploited this superstition and are contributing to the decimation of numerous animal species.

High-tech equipment seeks out promising molecules

Modern biomolecular and genetic techniques now make it possible to identify promising marine substances very rapidly. We have long known that the oceans are awash with unfamiliar bioactive substances that have healing or other beneficial properties. In many cases researchers have been able to ascertain the roles played by certain

substances within the living organisms – the immune system for instance – and to explain the biochemical processes that occur. They believe that many new agents will be found in the sea and in marine organisms in future, since the oceans are home to millions of plants, animals and bacterial strains. Today there are approximately 10,000 known natural substances, most of which were isolated from marine organisms over the past 20 years. New technology such as nuclear magnetic resonance, which can be used to identify and analyse unknown molecules, even if the organism contains only a trace of them, has made the search much easier. More research is now being conducted on the ocean floor than ever before. Unmanned submersible robots are capable of diving to depths of several 1000 metres to take samples.

In spite of these advances and the enormous biodiversity in the oceans (Chapter 5), few marine substances have so far been officially approved for clinical use. A new substance must not only attack the molecules that are key to the disease process, but it must also not interact negatively with food or other medication taken at the same time. It must also be capable of manufacture on a large scale.

Active agents from the sea – perfect for people

The appeal of most of the marine substances already approved lies in their potency. They are valued because they are produced from different source materials and compounds than their land-dwelling counterparts. The special structure of the molecules and components such



9.2 > Europe did not rediscover the benefits of the sea until the late 19th century. People living inland began to travel to the coast for rest and recuperation – as here on the East Frisian island of Norderney, off the North Sea coast of Germany.

as bromine and chlorine apparently help to make them so effective. The substances are not normally used in their pure form. First the molecules must be chemically modified and tailored to the human metabolism. The following marine substances are either already in clinical use or show promise for the future:

Nucleosides

Some of the best-known natural marine products are the unusual nucleosides spongouridine and spongothymidine derived from the Caribbean sponge *Cryptothetys crypta*. These have been in clinical use for more than 50 years. Nucleosides are components of DNA. For a cell to divide it must first replicate the DNA in its genetic material, incorporating the nucleosides precisely into the new DNA. Nucleosides contain a sugar component, usually ribose. Spongouridine and spongothymidine,

however, are arabinose-containing nucleosides. When these exogenous nucleosides are incorporated in the DNA, they inhibit the replication of genetic material, which is known as nucleic acid synthesis.

It was not long before this principle was being used to treat cancer and viruses because tumour cells divide extremely quickly, and even viruses need an active DNA synthesis in the cell to proliferate. Administering substances that interrupt the nucleic acid synthesis can greatly inhibit tumour growth. Thus the sponge nucleosides were developed into a substance for this particular purpose, a cytostatic drug. They were the basis for the synthesis of Ara-C (Cytarabine®), the first marine-derived drug approved by the U.S. Food and Drug Administration (FDA), in 1969. The virostatic agent Ara-A (Vidarabin®), which inhibits the proliferation of viruses, was approved in 1976, and is still used today to treat serious herpes simplex infections.



9.3 > Many effective agents are derived from marine sponges. Substances from the Elephant Ear Sponge *Lanthella basta* inhibit tumour growth. This sponge is abundant in the waters off the coast of Australia or Indonesia.



9.4 > Scientists first isolated prostaglandins from the coral *Plexaura homomalla* in the 1960s. This coral is found in the Caribbean and the western Atlantic Ocean at depths of up to 60 metres.

Prostaglandins

In 1969 it was established that *Plexaura homomalla*, a common coral found in the Caribbean and the western Atlantic, is a rich natural source of prostaglandins. Prostaglandins are important hormones produced from tissues that control essential body functions such as blood clotting and extremely complex inflammatory responses. The coral prostaglandins from *Plexaura homomalla* and other species have been researched exhaustively and have provided vital knowledge on the prostaglandin metabolism of humans. No drugs have yet resulted from this research.

Peptides

It took nearly 30 years after the development of Ara-C for the next marine-derived substance to be approved for the treatment of human medical conditions. This was the peptide Ziconotide (Prialt®), which is derived from the venom of various species of marine cone snail. Peptides are large protein components. Accordingly, the cone

snail toxin consists of a highly complex mix of different protein components called conotoxins. These conotoxins attack the metabolism of animals and humans at different points. In their natural environment the toxins paralyse their prey by blocking ion channels in the cell membrane – small apertures that are important to the transmission of nerve impulses. Instead of the pure snail venom, a modified version of the venom cocktail is used to treat severe chronic pain. The drug Ziconotide prevents ions from entering pain-sensing nerve cells. By doing so it blocks the nerves in the spinal cord that send pain signals to the brain. This drug is used for patients whose pain is so severe that it cannot be controlled by morphine medication. It is also used in cases of morphine-intolerance.

Alkaloids

Ecteinascidin 743 (also known as trabectedin) is an alkaloid, or nitrogen-containing organic compound marketed under the brand name of Yondelis®. It is the latest marine-derived compound and was originally extracted from the tunicate *Ecteinascidia turbinata*, a simple filter



9.5 > Cone snails such as *Conus textile* mainly inhabit tropical marine areas. They inject venom into their prey with a harpoon-like tooth. Scientists have succeeded in deriving a very effective painkiller from this venom.

feeder living on the sea floor. The substance was only approved as a drug in 2008. Ecteinascidin 743 interferes with a complex metabolic mechanism that confers drug resistance on cancer cells. It binds in the minor groove of DNA, slightly distorting the shape of the DNA, which obstructs the metabolism of the cancer cell. In greater detail, ecteinascidin 743 unites with the DNA repair protein TC-ER, then links with the DNA, thus preventing the MDR1 gene (MDR = multi drug resistance) – vital to the cancer cell – from being selected. This gene contains the blueprint for the MDR1 protein, the function of which is to discharge toxins and exogenous substances from cells. In cancer therapy, therefore, its effect is counterproductive because it also discharges medication from the tumour cells. This can ultimately lead to resistance and failure of the therapy. Ecteinascidin 743 blocks the production of MDR1 and thus prevents it from discharging the drug. Scientists hope that ecteinascidin 743 will reinforce the potency of other chemotherapy drugs by preventing resistance. Yondelis® has so far been approved for the treatment of soft tissue sarcomas – rare, malignant connective-tissue tumours.



9.6 > Moss animals are tiny animals that live in branch and leaf-like colonies. Bryostatin – an inhibitor of tumour cell growth – is extracted from the bryozoan *Bugula neritina*. It is probably produced by bacteria on the surface of the colony.

Other cancer drugs from the deep

A number of other marine anti-tumour agents are currently under study in clinical trials. They include bryostatin extracted from the bryozoan *Bugula neritina*, squalamine lactate from the spiny dogfish *Squalus acanthias* and sorbicillactone which comes from bacteria present in sponges.

Substances such as dolastatin 10 and dolastatin 15 isolated from the *Dolabella auricularia* snail and their progeny appear less promising. Clinical studies show that these anti-cancer agents alone are not capable of healing breast cancer or pancreatic cancer. They could conceivably be effective, however, when combined with other preparations.

What is the true potential of marine substances?

Many substances derived from the sea are already in commercial use as pharmaceutical drugs. Others have future potential. The following are some interesting

9.7 > Scientists have successfully extracted many active agents from organisms that live in the sea or fresh water. Some substances have already been developed into drugs.

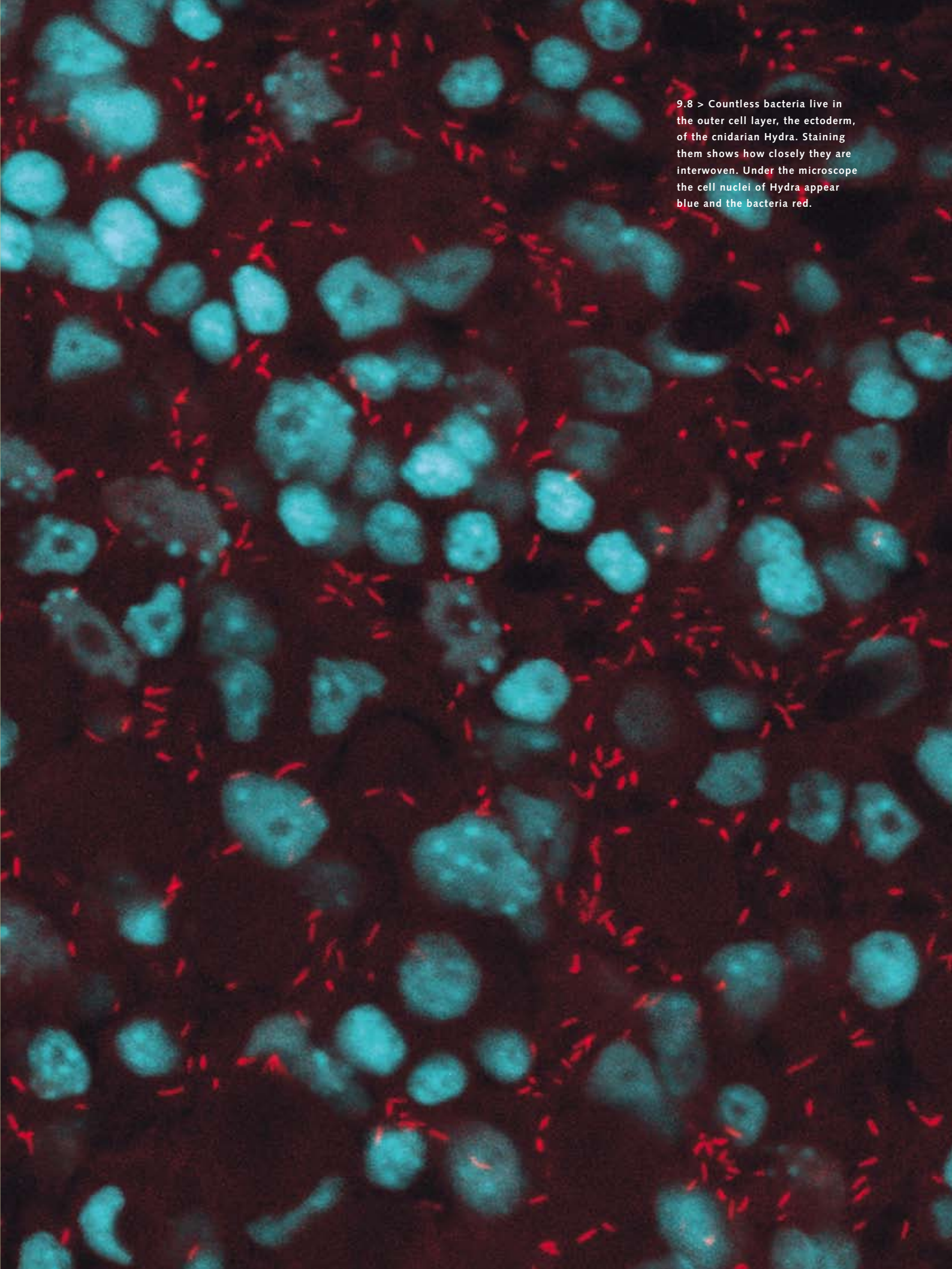
Isolated substance	Class	Primary effect	Application	Source of organism
Ara-A	Nucleoside	Inhibits viral replication (Virostatic agent)	Herpes simplex virus infections	Sponge
Ara-C	Nucleoside	Inhibits tumour growth (Cytostatic agent)	Leukaemia	Sponge
Ecteinascidin 743	Alkaloid	Obstructs tumour drug resistance	Soft tissue sarcomas (malignant connective tissue tumours)	Tunicate
Hydramacin (not yet approved)	Peptide	Antimicrobial effect	To fight penicillin resistant bacteria	Fresh water polyp
Ziconotide	Peptide	Obstructs ion channels	Painkiller	Sea snail

theories and questions on the future of research into marine substances:

1. The sea provides prime candidates for new medications. But locating them and then producing them on a large scale is not easy. This, on the one hand, is because the living organisms are difficult to find in the endless expanses of the ocean, and they often occur in very limited quantities. On the other, it is impossible to keep many of these organisms under laboratory conditions for long periods, or to cultivate them. For many years the pharmaceutical industry has had automated procedures in place for analysing variations of known substances and testing their suitability as drugs. This high-output screening allows researchers to test entire catalogues of related substances very rapidly. However, the molecular structure of marine substances is often so complicated that, even after being proved effective, they cannot easily be replicated or modified. This is what makes them so difficult to locate and develop.

Finding them is also an extremely time-consuming process that requires expensive equipment. The time and

effort involved are usually considered too great by the industrial sector. For this reason, most marine substances have thus far been discovered, isolated and analysed by researchers at scientific institutes. Moving the substance from the laboratory to the marketplace can also prove difficult – partly because patent law can create a barrier between universities and industry. The researcher would like to publish his findings. But the industrial sector wants to keep the agent and the drug formula secret, for fear of competition. Professional articles published too soon can also obstruct patent approval. This is why the pharmaceutical industry has long overlooked the ocean as a major and important source of new drugs. But industry and academia are now collaborating in promising new ways, such as the creation of start-up ventures. During the past few years these kinds of young businesses have sparked important new initiatives in this field. A vital question will be how to fund these risky schemes, and how appealing such individual paths out of academic research are likely to be considering the overall economic situation.



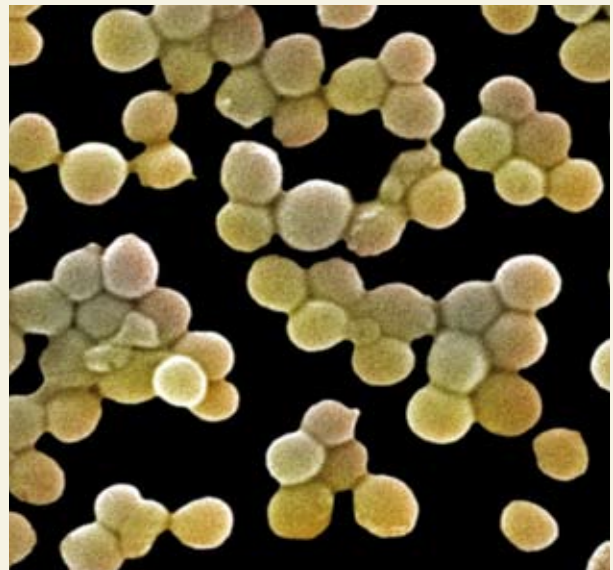
9.8 > Countless bacteria live in the outer cell layer, the ectoderm, of the cnidarian Hydra. Staining them shows how closely they are interwoven. Under the microscope the cell nuclei of Hydra appear blue and the bacteria red.

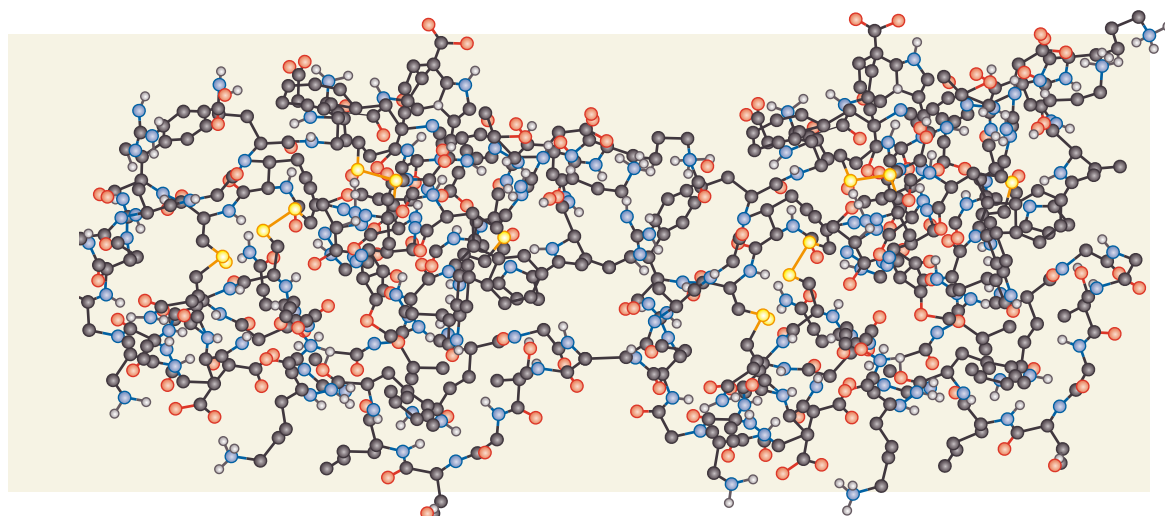
The fight against antibiotic resistance

The number of antibiotic-resistant bacteria has increased dramatically over the past 10 years. People who become infected with such bacteria can be extremely difficult to treat as scarcely any medication will help. Highly virulent is the methicillin-resistant *Staphylococcus aureus* (MRSA), a widespread bacterial strain resistant to the classic antibiotic methicillin, which has been prescribed for 50 years. The strains known as *Enterococcus faecium* and *Enterococcus faecalis*, resistant to the established substance vancomycin, are also problematic. Both types of bacteria are found in the healthy intestinal flora of humans, but pathogenic (disease-causing) varieties also exist. Virtually no antibiotic is effective against these bacteria. It is quite conceivable that the answer to this problem may be found in marine substances. For instance, cnidarians – a phylum of organisms that include jellyfish and are found both in seawater and freshwater – appear to be a very rich source of antimicrobial substances that specifically target certain bacteria. One of these substances is hydramacin, a peptide derived from the polyp Hydra, a tiny cnidarian armed with tentacles. Hydramacin kills off a range of germs that are resistant to penicillin – including certain strains of *Escherichia coli*, intestinal bacteria, as well as *Klebsiella oxytoca* and *Kleb-*

siella pneumonia, bacteria that inhabit the gastro-intestinal tract and can trigger diseases such as pneumonia and septicemia (blood poisoning). As bacteria can scarcely develop a resistance to hydramacin as they can to conventional antibiotics, it is currently seen as a promising model organism for a new generation of antibiotics. Cnidarians are so interesting that their tissue has now been systematically tested for novel antibiotics that can kill multi-resistant bacteria. This process has yielded another antimicrobial peptide, arminin, which has been used to produce a synthetic molecule. The resultant molecule is potent against many of the pathogens mentioned here. But that's not all Hydra can do: Hydra's immune system also contains a serine protease inhibitor, which has proved highly effective against *Staphylococcus aureus*. This substance inhibits serine proteases, proteins that control essential metabolic processes such as blood clotting. The discovery of this antimicrobial serine protease inhibitor in the Hydra polyp shows that evolution has developed different ways for organisms to defend themselves against bacteria. It also gives credibility to the assumption that substances extracted from marine animals can be turned into new classes of highly-efficient anti-staphylococcus antibiotics.

9.9 > Over time the iridescent gold-coloured *Staphylococcus aureus* bacteria have developed a resistance to the classic antibiotic methicillin. Infections with these bacteria are extremely difficult to treat.





9.10 > Biomolecules of water organisms such as hydramacin isolated from the Hydra polyp are often complex. This makes them difficult to reproduce in the laboratory.

2. Which organism is the actual source of the marine substance is not always clear-cut. Many substances have been isolated from invertebrates in the past. In many cases, however, these did not originate from the animal itself but from the bacteria or fungi living in or on it. Microorganisms can make up as much as 40 per cent of the biomass of sponges, many of which are also colonized by microalgae. It is crucial to know when microorganisms are the actual producers of the agent, because it is hoped that they are more easily cultivated under laboratory conditions than the sea-dwellers upon which they colonize. It was initially believed that harvesting sponges and other animals on a grand scale was possible, but it soon became clear that the species could easily be completely wiped out. The focus then shifted to breeding bacteria in the laboratory, a process which is seldom successful. In some cases researchers have achieved results, however. For instance, large quantities of sorbicillactone, a substance mentioned above, were extracted within a short time from fungal cultures derived from sponges. Nevertheless, the difficulty remains that cultivating unknown bacteria can be a time-consuming process.

3. Today the search for new substances is facilitated by culture-independent methods of genetic analysis. This does away with the painstaking and complicated laboratory culture of bacteria and other organisms. For many decades expensive chemical and biochemical analyses

alone were used to verify the presence of effective substances. Today, thanks to modern genetic analysis, this can be done much more quickly and easily. The latest procedures search the genetic material of marine organisms for conspicuous gene segments that contain the blueprint for promising enzymes. Such enzymes are the tradesmen of the metabolism, building different substances. The development of such DNA-sequencing techniques is definitely the greatest advance in substance research of recent years. Large-scale sequencing projects can now trawl through the genetic material of thousands of marine organisms within a short time, searching for promising gene segments. One example is the Global Ocean Sampling expedition by the J. Craig Venter Institute in the USA, which played a significant part in decoding the human genome a few years ago. The focus of this institute is now turning increasingly to the sea. Its objective is to search the genetic material of marine organisms for economically significant metabolic pathways. Entire habitats can be subjected to sequence analysis. Such major projects process both the organisms and the microbes growing on them at the same time. Therefore the findings can no longer be attributed to individual species, but the researchers anyway are mainly preoccupied with learning about the genetic make-up of an entire habitat within a short time, and finding out whether that location harbours any interesting substances at all.

Searching for the causes of disease

> The immune systems of humans and animals are remarkably similar, so much so that comparing them has become a prime subject of scientific study. Researchers hope that examining simple marine organisms will lead to a better understanding of immunity disorders of the bowel, skin and lungs. It is safe to say that bacteria play a major role here – not only as pathogenic agents, but especially as an element of the body's defence system.

How does an organism protect itself from pathogens?

The first line of defence against potential pathogens in humans, other vertebrates, and invertebrates such as sponges, is natural immunity. Even infants have an innate immune system, although they have hardly been exposed to any pathogens. This ancient phylogenetic defence mechanism consists of scavenger cells that destroy germs (phagocytosis), metabolic processes that attack and dissolve foreign proteins, and the production of antimicrobial peptides. These peptides are found in animals, plants and microorganisms. They are produced by certain body tissues such as the intestine, skin and lungs, and provide protection against infection. The human immune defence system – or at least part of it – is very old and is related to the lower-order organisms. These organisms include sponges and cnidarians (corals, jellyfish, sea anemones and freshwater polyps), which have lived in the sea for hundreds of millions of years in constant contact with bacteria and viruses. For this reason it is quite possible that they can teach scientists how an efficient defence system develops and how it can be mended in the event of disease.

Cnidarians, among the most primordial of sea-dwellers, seem ideally suited to the study of how an organism keeps bacteria and other pathogens at bay. They are relatively simple organisms, but nonetheless numerous complex metabolic processes take place within and between their body cells. At first glance cnidarians appear to be vulnerable and defenceless against pathogens because they have neither immune cells to destroy pathogenic

intruders nor a lymphatic system to circulate defence cells through the body. They also lack a solid protective covering, having only an outer layer of cells, the epithelium. They have nonetheless managed to survive for millions of years. This makes them extremely interesting subjects of study.

Researchers are trying to find out how their tissue interacts with microbes, and how the metabolic processes in their outer skin fend off enemies. They have successfully bred genetically-modified cnidarians in which the antibacterial defence molecules are visible. This enables them to examine the living creature to see both where the antibodies are released and where they are deployed. It seems amazing that such weak and insignificant little creatures can survive in an environment that is literally teeming with potential pathogens, despite their lack of an immune system and patrolling immune cells. As we know, the exterior surface of many marine creatures, such as sponges, is permanently colonized by bacteria. And furthermore, a litre of seawater can contain up to 2 trillion bacteria and an even greater number of viruses. These microorganisms include many potential pathogens. Despite all this the creatures survive. If we wish to gain greater insight into how the body interacts with its environment, and to explore the principles of evolution, ancient marine organisms seem to be the ideal models.

Thanks to new analytical capabilities, cnidarians play an interesting role in trying to understand the evolution of immune reactions, identifying the genes involved and explaining the universal mechanisms of animal-micro-organism interaction.

Model marine organisms
Cnidarians and sponges are among the oldest life forms on Earth. They have been living in the oceans for hundreds of millions of years. In spite of their simple body structure they possess an amazing number of genes. These control metabolic processes that have been lost to some extent by higher organisms during the course of evolution. For this reason cnidarians and sponges can be viewed as a kind of prototype for all animals, and represent ideal models to study the basic principles of life.

The body and its bacteria – a finely-tuned instrument

Higher life forms and bacteria are in constant contact with each other. Bacteria act either as disease-causing pathogens or as symbionts that take over some vital functions. For example, the intestine is colonized by a complex and dynamic community of microorganisms that support a range of metabolic functions. The intestine is gradually colonized by bacteria from birth onwards, continuing through the early stages of life until each individual ultimately develops his or her own specific intestinal flora.

Questions that largely remain unexplained include how the intestinal epithelium (the outer cell layer) interacts with the microorganisms, how the body differentiates between useful bacteria and potential pathogens, and how the bacteria influence the metabolic processes and efficiency of the human intestinal epithelium. It is possible that studies of Cnidaria could help here. Their epithelium, or outer body surface, is also colonized by a complex and dynamic community of microorganisms. Tests on the freshwater polyp *Hydra* have shown that individuals from different *Hydra* species differ greatly in the composition of their microfauna.

Having said that, however, when the bacterial composition of individuals kept under controlled laboratory conditions for many years, are compared to individuals of the same species taken directly from their natural habitat, the results are strikingly similar. This means that the colonizing bacteria remain faithful to the *Hydra* individuals for long periods. They are constant inhabitants of the epithelium.

These findings suggest that a rigorous selection process is at work on the epithelium. It appears that under specific conditions, certain bacterial communities that are ideally suited to the habitat become established on the epithelial tissue, remaining constant for a long time. These observations as well suggest that the epithelium actively shapes the composition of the microbial community. In case the bacterial growth on mammals or invertebrates is removed, the animals usually fall ill. The



metabolic system is disrupted and the immune system weakened. Disorders of the alimentary canal are extremely severe. The animals can no longer defend themselves against infections caused by pathogenic bacteria and viruses.

We are also aware that certain genetic defects in the human immune system can disrupt the collaboration between the epithelium and its colonizing microbes. People affected are usually prone to inflammatory diseases of the barrier organs – the parts of the body that are open to the outside world, such as the skin and lungs. Although we have no definite immunobiological explanation for the effect of the microbes, it is clear that symbiotic bacteria actively contribute to the critical balance between health and disease.

Bacteria are therefore essential to a large number of organisms. For instance, during its juvenile stage the bioluminescent squid *Euprymna scolopes* develops light organs on the surface of its skin. Like a firefly, the squid is therefore capable of generating light pulses by means of a biochemical reaction. However, the light organs cannot grow without a certain component being contributed by *Vibrio fischeri*, a symbiotic bacterium present in the epithelium of the squid. It is therefore clear that both the physical development and the immune system of verte-

9.11 > Sea anemones belong to the species-rich phylum Cnidaria. They are related to corals and jellyfish.

More than the sum of its parts – the holobiont

The healthy microbial fauna of human beings and animals is highly diverse. The genetic information contained in all these microorganisms is much greater than that in humans alone. For this reason we can regard the human body, together with all the species inhabiting it, as a rich ecosystem of microbes, single-celled organisms, and other organisms – as a super-organism, a holobiont. Some scientists argue that the microbiota is essential, not only to the immediate life of the host, but also to the host's evolution. This hypothesis implies that the holobiont, including all the microbes – not the human being or animal alone – should be regarded as a unit of evolution. We still have no idea of how the parts of this super-organism interact with each other, or how they influence health. We need to learn how the organisms cohabiting in the super-organism interact at a molecular level. How have the crucial genes of the many different species of the holobiont collectively evolved? How do the microorganisms ultimately influence the biology of their hosts, and how do the hosts influence the colonizing microbes?

How does the holobiont function? This is one of the most difficult questions to answer. Cnidarians and their efficient epithe-

lial defence systems appear to be valuable objects of study in the effort to tackle this question. The reason is that these simple organisms contain many old genes that no longer exist in higher animals such as the fruit fly *Drosophila melanogaster* or the roundworm *Caenorhabditis elegans*, which have already been studied extensively by geneticists. If we wish to understand primary metabolic processes and the principles of immune response, cnidarians would therefore be the creatures of choice. It is also interesting to note that the microbial community colonizing the freshwater polyp *Hydra* are extremely complex and yet exactly tailored to *Hydra*. They clearly differ from the microbes living in the surrounding waters. Each species of *Hydra* has its own microbial menu, which is very stable and scarcely changes. The microbial fauna very likely takes over a range of metabolic functions for the host. Disturbing the balance between *Hydra* and its colonizing microbes appears to pave the way for disease. Studying host-microbe interactions in *Hydra* is of fundamental interest to researchers because it helps them understand the molecular language between host and microbes in the collective ancestor of all mammals, and thus to unravel the causes of human disease.



9.12 > Single-celled algae live in a symbiotic relationship with corals, feeding them with the byproducts of their photosynthesis. When these algae die off, the corals turn white, a process called coral bleaching. One cause may be an abnormal change in bacterial growth.

brates and invertebrates are significantly affected by their colonizing microorganisms. However, little is understood about how bacteria influence the immune functions and the mechanisms that control the complex interactions between the microbial communities and the animals.

Neither do we know how the metabolism of the epithelium impacts the composition of the symbiotic bacterial community. Initial experiments on the polyp *Hydra* showed that changes to the cells do in fact alter the bacterial flora. When a certain type of cell was removed from the tissue, the bacterial composition on *Hydra*'s body surface changed conspicuously. The marked decrease of normally predominant proteobacteria was accompanied by a similar increase in the formerly rare bacteria of the bacteroidetes group. There certainly appears to be a direct interaction between the host epithelium and the microbes.

A new understanding of human disease

A large number of modern human diseases stem from dysfunctions of the boundary between the body and the outside world. These include chronic inflammatory diseases of the barrier organs, those organs that are in contact with the external environment – the skin, the lungs and the intestine, which is fed from outside sources. Examples are bronchial asthma (lungs), psoriasis and neurodermatitis (skin) as well as Crohn's disease and ulcerative colitis, chronic inflammatory bowel diseases (intestine).

Interestingly, these conditions are entirely unknown in animals. Systematic genetic tests have shown that many of them are triggered by so-called risk genes, which are ancient in an evolutionary sense. It is ironic that such complaints have proliferated in recent years, especially in the industrial nations. All diseases have one thing in common, that the human immune system breaks down at the barriers to the environment, and attacks its own body structures. New technologies have enabled us to trace individual abnormal elements on the molecular roadmap for disease. These individual components should now be combined to create an overall model for under-



standing the mechanisms underlying malfunctions of the immune system.

Current research indicates that immune system malfunction involves a large number of genes that control the evolutionarily old forms of immunological engagement with the environment, such as the surrounding microbiota.

One question is how, during the course of evolution, genetic variability could occur in those genes that determine the characteristics of the barriers. How do erratic food conditions or different microbiota in the water change the genetic variability of the barriers? How do such changes influence the evolutionary fitness of organisms or, in other words, the likelihood of genes surviving and reproducing? Understanding the processes on the surface of marine animals may help us to comprehend how diseases of the barrier organs occur in humans. Once we have unravelled the evolution and function of the barrier organs, we may find new strategies to treat or even prevent these diseases. Over past decades selected model organisms such as the mouse and the fruit fly *Drosophila melanogaster* have taught us a lot about recognizing and fighting the triggers of disease. But even today the question of why the outer skin of all organisms is colonized by microbes and how these microbes interact with the host remains a mystery.

9.13 > The polyp *Hydra*, a cnidarian, is an ideal model organism. It is resilient and regenerates rapidly. Its reproduction process is also uncomplicated, with one method being to simply form a round polyp bud on the side of its body.

Legal issues in marine medical research

> In response to the growing interest in marine substances, legal scholars are trying to clarify which state has the right to exploit these resources. The main issues concern where the organisms are found, and the extent to which a natural substance or gene sequence can be patented. The fact that different patenting rules apply in different parts of the world further complicates matters.

What makes the substances so interesting

Interest in the genetic resources found on the deep seabed has increased dramatically in recent years. They include microorganisms which occur in enormous quantities around hydrothermal vent sites, known as black smokers (Chapter 7) on the ocean floor. In complete darkness the microorganisms produce biomass from carbon dioxide and water. The energy they need for the conversion of carbon dioxide is extracted/obtained from the oxidation of hydrogen sulphide that discharges from the sea floor via the black smokers. Experts call this type of biomass production “chemosynthesis”. In contrast, plants produce biomass by photosynthesis, which is driven by energy-rich sunlight.

Chemosynthetic bacteria are of great interest, as they possess unique genetic structures and special biochemical agents which could play a key role in developing effective vaccines and antibiotics, or in cancer research.

It would also appear desirable from the industrial sectors point of view to exploit these organisms. After all, the bacteria which are active at the black smokers can tolerate high water pressures and extreme temperatures. Heat-stable enzymes have now been isolated from these resilient extremophilic bacteria and could potentially be used by industry. For instance, many manufacturing processes in the food and cosmetic industries operate at high temperatures, and heat-resistant enzymes would greatly simplify these. The ability to convert and thus detoxify deadly poisonous hydrogen sulphide into more benign sulphur compounds makes the chemosynthetic bacteria even more attractive.

Who “owns” the marine substances?

Against this background, one key question arises: who has the right to utilize and research the genetic resources of the deep seabed? International law initially differentiates only according to country of origin. If a scientific research institute applies to collect samples of deep sea organisms during an expedition, its activities are attributed to the flag state of the research vessel. Alternatively, the country of origin of the syndicate or biotechnology enterprise involved is the determining factor.

Where the sample microbes are to be taken from is also relevant. According to the United Nations Convention on the Law of the Sea (UNCLOS) (Chapter 10), marine scientific research in the exclusive economic zone generally requires the consent of the coastal state. Provided these are required purely for research purposes, the coastal state should allow third countries to take samples from the waters over which it exercises jurisdiction. In the event that the research findings could ultimately have commercial potential (bio-prospecting), the coastal state may exercise its own discretion. In case of doubt it may withhold its consent to the conduct of the activities in its waters. This applies particularly to measures which are of direct economic significance, such as the exploration of natural resources: in other words, exploring the seabed with the intention of exploiting its resources.

In the case of maritime regions beyond the limits of national jurisdiction, the legal situation is less clear-cut. Who has the right to exploit the biological resources of the high seas, and the legal provisions that should govern such activity, have long been matters of dispute within



9.14 > Some microbes, e.g. the single-celled archaea, live in the vicinity of hot springs. Some contain substances which lend themselves to industrial production. Certain marine bacteria can be used to manufacture polymers, special synthetics which could even be utilized for future cancer therapy.

the international community. This includes those areas far from the coast where the black smokers are to be found, such as the mid-ocean ridges. The problem is that none of the international conventions and agreements contains clear provisions on the exploitation of genetic resources on the ocean floor. For this reason one section of the international community considers that they should be fairly shared between nations. The other, however, believes that any nation should have free access to these resources. Clearly, these views are diametrically opposed.

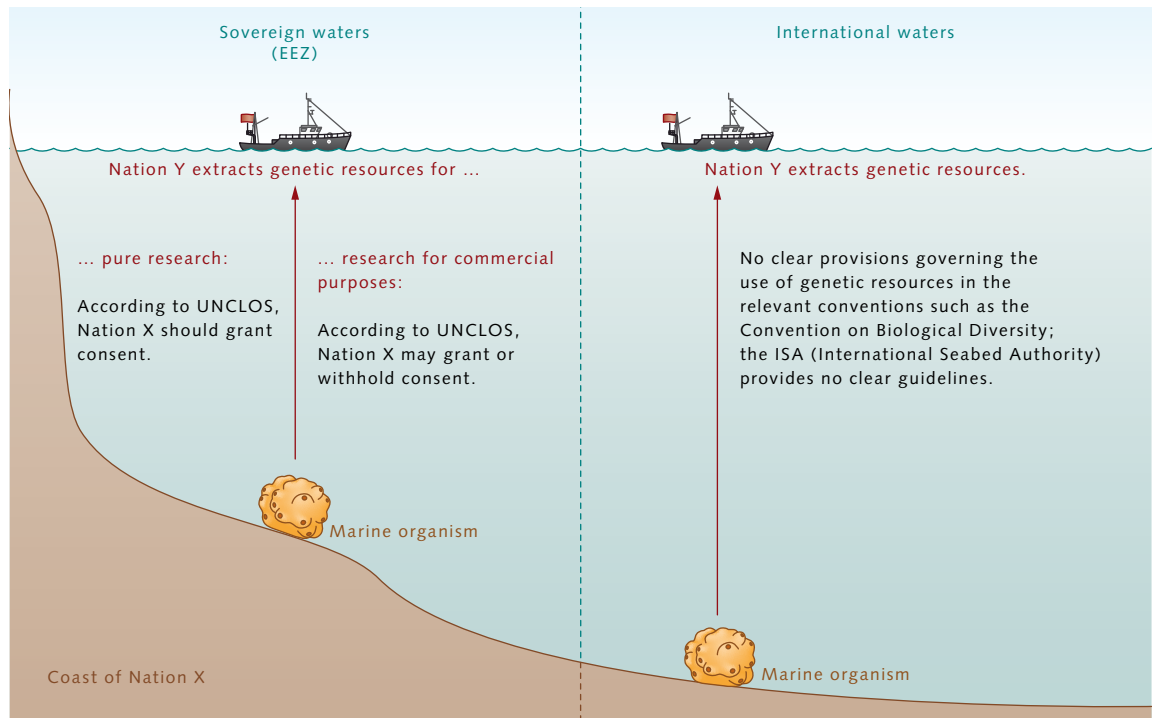
With regard to the deep seabed, the United Nations Convention on the Law of the Sea (UNCLOS) stipulates that “the area of the seabed ... beyond the limits of national jurisdiction, as well as its resources, are the common heritage of mankind”. But this provision applies only to mineral resources such as ores and manganese nodules. If a state wishes to exploit manganese nodules on the deep seabed (Chapter 10), it must obtain a licence from the International Seabed Authority (ISA) and share the

benefits with the developing countries. This explicit provision does not apply to genetic resources on the deep sea floor, however.

On the other hand, the Convention on Biological Diversity (CBD) adopted in Rio de Janeiro in 1992 calls for “the fair and equitable sharing of the benefits arising out of the utilization of genetic resources”; in other words, nature’s biological bounty should be shared fairly between the industrialized nations and the developing countries. However, this objective refers only to the area within the limits of national jurisdiction and not to maritime regions far from land.

So the situation remains unresolved, with each side interpreting the content of UNCLOS and the Convention on Biological Diversity according to its own best interests. The situation is further complicated by UNCLOS allowing yet another interpretation. It establishes the “freedom of the high seas”, under which all nations are free to utilize resources and carry out research at will. This includes the right to engage in fishing in international

9.15 > Regulation of the exploitation of genetic resources on the seabed has so far proved inadequate. A state may withhold consent within its EEZ. There are no clear guidelines governing international waters, which can lead to conflict between states.

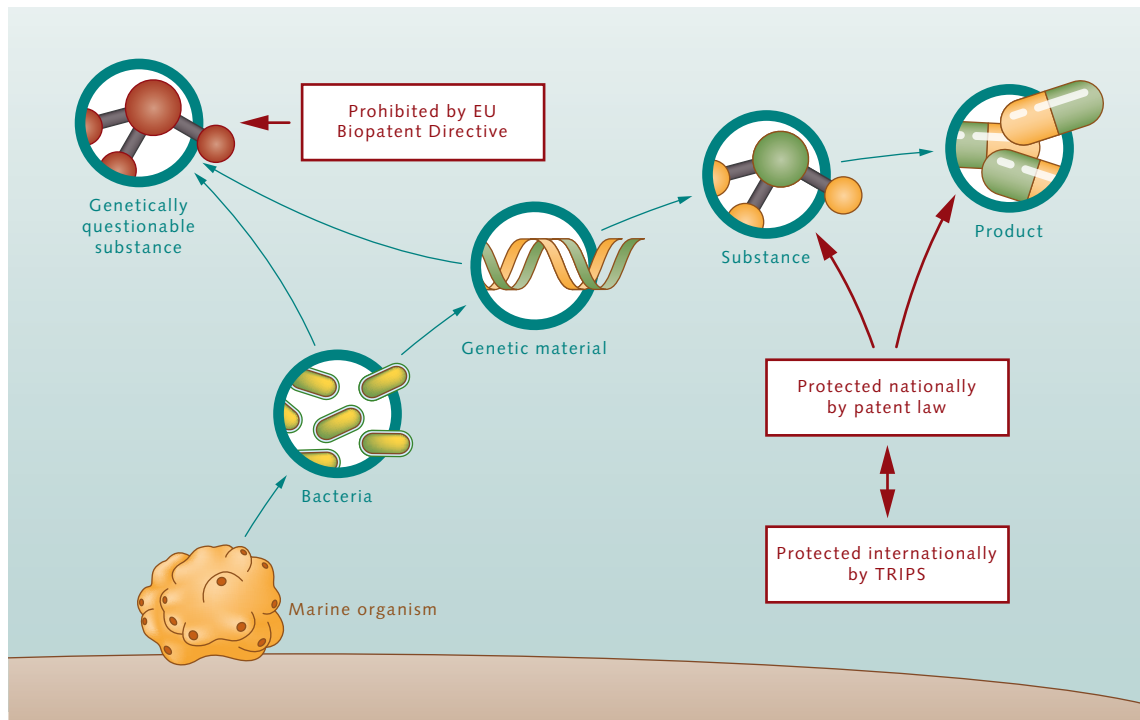


waters. All states are entitled to take measures for “the conservation and management of the living resources of the high seas”. As the regime of the high seas under UNCLOS also covers the deep seabed and to the extent to which the convention does not contain any special rule to the contrary, this implies that the biological and genetic resources there are no less freely available than the fish. As a result all nations should be at liberty to research and utilize the genetic resources found on the deep seabed. This opinion is shared by most members of a special United Nations working group set up by the United Nations General Assembly in 2005 to address the protection and sustainable use of marine biodiversity beyond national jurisdiction.

Other members of the UN working group are opposed to this interpretation. As mentioned above, they want the biological resources – similar to minerals – to be shared equally between the individual states. The impasse has triggered heated debate at international meetings of the UN working group, and agreement is not

expected any time soon. It is likely that at least one of the two conventions would need to be amended, and there is little chance of this happening at present.

There could be another solution, however. Some experts argue that neither UNCLOS nor the Convention on Biodiversity should primarily apply to genetic resources. Ultimately this is not about harvesting resources such as fish, minerals or ores from the seabed. It is about searching for substances in a few organisms, using these substances to develop new drugs and, later, manufacturing the drugs in industrial facilities. Strictly speaking, therefore, it is the information itself contained in the ocean organisms which is of interest, not the organisms themselves. Arguably this is more an issue of intellectual property than the traditional exploitation of natural resources – indicating that patent law would most closely fit. There is a lot to be said, therefore, for leaving international marine and environmental law as it stands, and liberalizing the provisions of international patent protection.

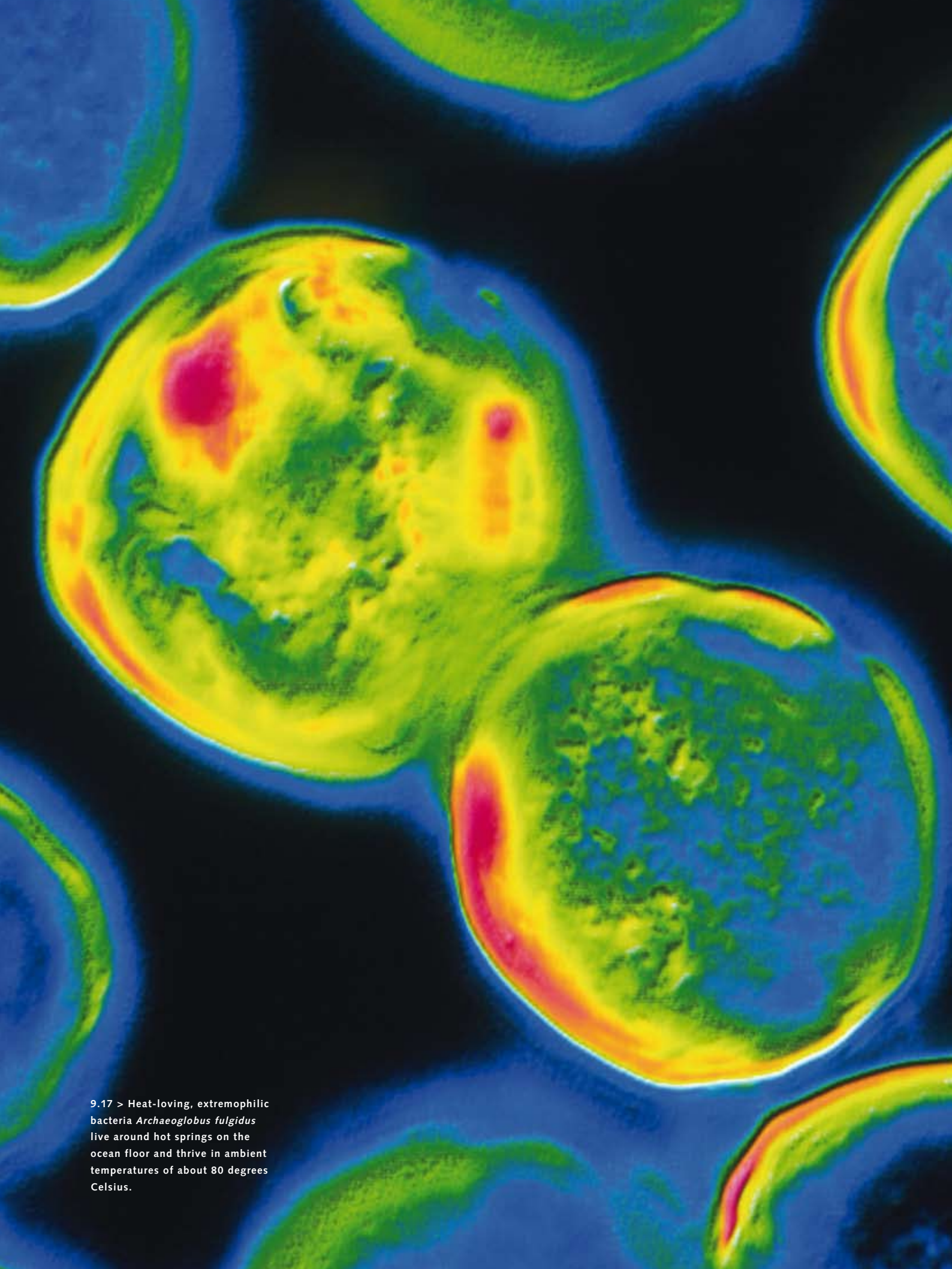


9.16 > National and international patent law governs the exploitation of natural resources and genetic information from living organisms. Substances extracted from organisms are patentable. The same applies to individual isolated gene sequences and genetically modified organisms. Newly-discovered species of animal and all their genetic material, however, cannot be patented.

The limits to patent law

If the search for marine substances touches on legal issues, then it is important to settle the question of how the research findings may be commercially utilized and exploited. In principle, patent protection of utilization and exploitation rights is governed by the provisions of domestic law. In Germany these are anchored in the Patent Act (PatG). In general this Act protects inventions, including findings from genetic research. The protection afforded by this Act ends at Germany's national borders. International protection of intellectual property is provided by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which applies within the sphere of influence of the World Trade Organization (WTO). The TRIPS agreement provides for mutual recognition of intellectual property rights by the signatories provided that these rights are protected by national patents. The intellectual property of all TRIPS signatories is thus protected.

Patentable objects basically include any microorganisms, animals or plants modified in the laboratory, such as genetically-modified varieties of maize. They may also be elements isolated from the human body or otherwise produced by means of a technical process, especially living cells, including the sequence or partial sequence of a gene. The discovery of a new species, however, is not patentable as a species cannot be patented as a matter of principle. On the other hand, biological material found in nature or the genetic code can be considered new in terms of patentability if it is isolated by a technical process and, by written description, is made available for the first time. Every state has the right to exclude from patentability animals, plants and the biological processes used to breed them – such as new breeds of animals, as has occurred in Germany with the Patent Act and in the EU with the Biopatent Directive. The same applies to other inventions and individual DNA sequences where economic exploitation is to be prevented for reasons of ethics and security, such as the cloning of human embryos.



9.17 > Heat-loving, extremophilic bacteria *Archaeoglobus fulgidus* live around hot springs on the ocean floor and thrive in ambient temperatures of about 80 degrees Celsius.

According to the TRIPS Agreement, commercial exploitation may be prevented when, in the opinion of the state concerned, this is necessary for the protection of “ordre public or morality; this explicitly includes inventions dangerous to human, animal or plant life or health or seriously prejudicial to the environment”. According to the Biopatent Directive adopted by the EU in 1998, inventions are not patentable if their commercial exploitation may offend against ordre public or morality. This includes processes for cloning human beings and uses of human embryos for industrial or commercial purposes.

The different institutions are divided on the question of how far patent protection of DNA sequences should go. In the EU, protection is limited to the functions of the sequence or partial sequence of any gene described in

the patent application. In contrast, in the USA the principle of absolute protection applies, without limitation to the functions described by the inventor. This means that in the USA not only the invention explicitly described in the application is protected by patent law, but also any developments and products which may follow in future. US patent law is therefore much more comprehensive than its European counterpart, but both approaches are compatible with international provisions. The different concepts constantly lead to controversy. The level of protection afforded by patent law to marine-derived drugs, too, will vary from region to region. This situation is unlikely to change in the near future. Behind this argument lie historic and cultural differences in concepts of individual freedom and a government's duty to protect.

CONCLUSION

The dawn of a new era?

The extraction of marine substances for medical or industrial use is attracting greater interest from both scientists and the business sector. In recent years a range of substances has been derived from marine organisms which are now used in cancer therapy and the treatment of viral infections. Modern methods of genetic analysis greatly simplify the search for substances – because they by-pass the need for laborious cultivation in laboratories. Businesses long hesitated to become involved in the expensive search for marine substances, and this remained the province of academic institutions. But as young start-up businesses become established, the commercialization of marine-derived drugs is gaining momentum. However, the lack of venture capital providers often leaves a substantial innovation gap between pure research and the pre-commercial development of a substance. Government funding could be crucial in helping to bridge the gap, especially during the long phase of clinical

testing. But it is not only the prospect of new substances which is making the exploration of marine organisms so interesting. It seems that the metabolic pathways of primitive marine organisms and humans are in many ways remarkably similar. Simple life forms such as sponges and cnidarians provide ideal models for understanding human biochemical processes and diseases. Research is focusing on disorders of the human barrier organs – the skin, lungs and the intestine. Experts believe that these are triggered when the human immune system and the symbiotic bacteria colonizing the body's surface are not interacting as they should. Here too cnidarians, as relatively simple host-bacteria systems, can provide new insights. We are certain that bacteria in the barrier organs play a major role in the critical balance between health and disease. But what exactly happens between humans and microbes is still virtually unknown territory, requiring years of research. Given the new interest in the topic, clarification is also needed on how the biological resources of the oceans should be shared between nations.

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