The importance of open-ended research and how valuable discoveries can turn up where no one ever thought to look

UNEXPECTED BENEFITS

THIS PROJECT IS FUNDED BY

The Kjell and Märta Beijer Foundation, the Olle Engkvist Foundation,
the Sven and Dagmar Salén Foundation and the Wenner-Gren Foundation.

OPEN-ENDED RESEARCH **allows for the unexpected and benefits society most**

We face major challenges in terms of health, the environment and economic growth. Research is crucial for coming up with new solutions. All too often, politicians and other decision-makers reason that strategic initiatives focusing on predetermined areas will deliver the necessary results.

With this approach, we are in danger of missing the greatest breakthroughs, which in many cases are based on discoveries in open-ended research. A curiosity-driven quest for basic knowledge may result in groundbreaking benefits, but these are often unforeseeable. They cannot be pinned down in strategic plans. Strikingly often, key discoveries are made by individual researchers or small research teams, rather than in purpose-built, top-down networks.

In the past few years, Sweden and other countries have made major efforts to boost innovation and what is seen as 'useful' research. Participating researchers have had to define in advance what they expect to achieve. This kind of regime may mean that research closes the door to unexpected discoveries that might otherwise arise — discoveries that can often prove more valuable than the original research ideas.

'Chance favours the prepared mind.' This was how the bacteriologist Alexander Fleming explained his decision not to discard the famous dish of contaminated, mouldy *Staphylococcus* culture. Instead, he realised that he was on the track of something interesting. The bacteria had died and, on further investigation, Fleming found an antibacterial substance formed by the mould fungus. It gave us penicillin, which saves millions of lives to this day and is often ranked as the most important discovery of the 20th century.

The Royal Swedish Academy of Sciences is alarmed by the decline of recent years in conditions for open-ended research, and strongly supports initiatives to improve its funding. Without such actions, the long-term development of society will be impaired. In this publication we aim to highlight a few examples of how basic research, without being driven by ideas about applications, has nonetheless yielded myriad everyday benefits. History is full of unexpected discoveries that paved the way for what are now self-evident features of our everyday life, such as our IT society, healthcare and drugs that keep us healthy, or new materials with fascinating properties.

WE WISH YOU AN ENJOYABLE — AND PERHAPS SURPRISING — READ!

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MODERN BIOTECHNOLOGY HAS FOUND numerous valuable applications in various fields. Genes implicated in cancer can be identified; plants can be modified to produce useful substances; and traces of DNA can link a perpetrator with a crime scene. Somewhat surprisingly, the basis for these advances was research on thermophilic bacteria – research conducted with no inkling of its huge future importance or the vast profits it would mean for the biotechnology sector.

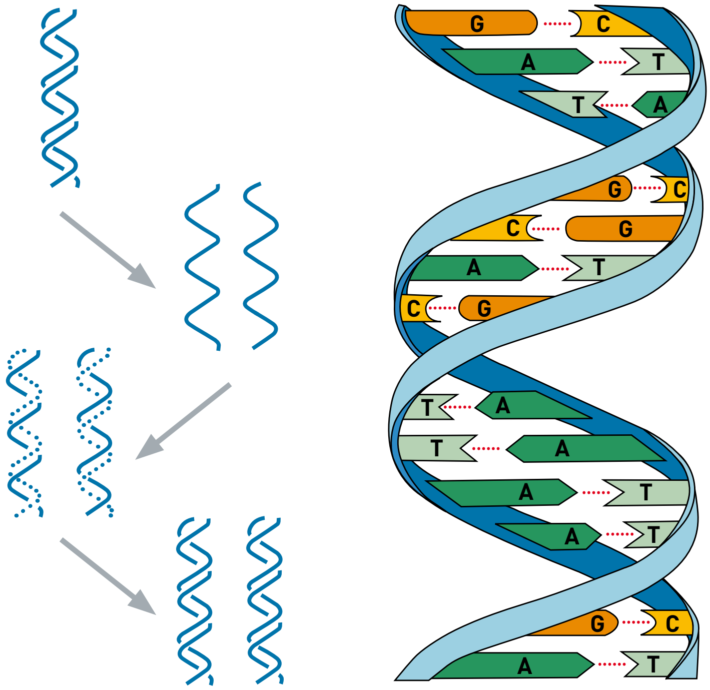
A QUEST FOR HARDY BACTERIA **MADE THE BIOTECHNOLOGY REVOLUTION POSSIBLE**

The hot springs of Yellowstone National Park get their beautiful colour from various bacteria. The discovery of the biological mechanism enabling them to survive near boiling-point was crucial for developing the PCR method of replicating DNA.

The ability to manipulate DNA molecules is the foundation of modern medical diagnostics, research on species development and a great deal more. The genetic code in an organism's genome governs production of various proteins that, in turn, drive countless biological processes. This knowledge has emerged and been refined in the past few decades. In the 1980s, scientists were already beginning to perceive its vast future potential. But existing techniques restricted what they were able to do. Basic tasks like obtaining large quantities of DNA to study called for growing bacterial cultures with the desired DNA fragments inserted into their genome. The method was complicated and required many purification stages before the scientists were able to extract the DNA clones they sought.

A better method was needed. But the spark that ignited the biotechnology revolution came not from purpose-oriented methodological development but from basic research on bacteria. The background dates back to the 1960s, when a microbiologist, Thomas Brock, was interested in the conditions for life. The prevailing scientific view was that no organisms could survive at high temperatures. At Indiana University, Brock began studying bacteria samples from hot springs in Yellowstone National Park. To his amazement, he found a species that could survive in near-boiling water; normally, after all, we boil water to kill any bacteria it may contain. The species was named *Thermus aquaticus*, and Brock's research brought about a new view of the adaptability of living organisms to extreme environments.

As often happens, however, the research considered 'useless' at the time later resulted in important applications. One biotechnologist in the 1980s who was frustrated with existing techniques was Kary Mullis, a chemist. He constructed DNA 'building blocks' and patiently joined them to make DNA fragments. The need for faster, automatic techniques was clear.



THE DNA MOLECULE IS FORMED FROM nitrogen bases that fit together in a specific pattern: adenine bonds to thymine and guanine to cytosine. If the two strands of the molecule are separated, each half can be filled in with new nitrogen bases, so that replication occurs. Half a century ago Francis Crick, James Watson and Maurice Wilkins, who were jointly awarded the 1962 Nobel Prize in Physiology or Medicine for their description of DNA, realised that the molecule had this power of self-replication.

Mullis came up with the polymerase chain reaction (PCR) idea in the course of a nocturnal drive in his home state, California. He was thinking about the simple way in which our cells repair damage in one of the DNA strands. A special enzyme captures the requisite building blocks and composes a new mirror image of the undamaged strand.

The stroke of genius in Mullis's thinking was the idea of copying a short DNA strand in a test tube and then heating it to cause the newly formed double strand to divide. The sample is then cooled and the process repeated to replicate the two single strands. When these are reheated, four single strands form. This multiplication can continue until there are millions of DNA fragments. The problem, however, was that this PCR method required the sample to be reheated to near boiling-point over and over again. The replication enzyme available to Mullis at that time was a protein that works best at our body temperature. If it gets much hotter, the enzyme is destroyed – it coagulates, just like the proteins in a boiled egg.

This is where the hardy bacterium *Thermus aquaticus* comes in. Its replication enzyme functions at high temperatures as well, and Mullis used it to develop the PCR method, for which he was awarded the 1993 Nobel Prize in Chemistry. Scientists were soon able, using simple equipment, to make bucketfuls of DNA within a few hours, and today this is helping to bring about new advances. For example, the treatment of certain illnesses can be adapted to genetic variation in different individuals; bacteria can be modified to produce hydrogen gas that gives us energy; and forensic technology can make increasingly effective and reliable use of DNA traces. All this is thanks to the survivors of the hot springs – and the fact that someone looked for them. //

Report

UNFORESEEN SIDETRACKS

led painless and

Dentistry has made tremendous progress in the past few decades. Today, access to proficient, painless dental care, whether it involves filling cavities or even replacing teeth with implants, is taken for granted. These successes are largely due to hardworking scientists who sought knowledge in quite different areas but, thanks to startling discoveries, paved the way for dentists' new tools.

to dentistry new teeth

The specialist dental clinic at St. Erik's Hospital in Stockholm, part of the Swedish Public Dental Service, is attended by people who need complicated root-canal fillings, restoration of an effective bite or replacement of lost teeth. Gunnel Hanses, one of the senior dentists, specialises in bite reconstruction and implants. She owes her ability to work wonders at her clinic to basic research in a range of areas far from dental care, carried out by, for example, chemists interested in plant substances, doctors studying blood flow and particle physicists in search of the basic building blocks of matter.

'We replace individual teeth or do full mouth reconstruction with whole rows of tooth implants. For this we use titanium implants that, amazingly, become fully integrated with the jawbone. In the many stages required, we also depend on modern X-ray technology and local anaesthesia. My colleagues and I use these every day and couldn't manage without them during the thousand or so interventions we do every year.'

For Hanses, the first step when a patient arrives is to take X-rays, in order to see how much bone tissue the jaw contains for attachment of the titanium screws. In an X-ray investigation, billions of tiny energy particles known as photons penetrate the jaw. Hard body parts like bones allow fewer photons to pass through than soft parts do. The relatively low density of a damaged area, such as a weakened jawbone or tooth decay, is revealed by the X-ray image. >>>

In retrospect, it's immensely exciting to look back on the technological advances that have taken place in dentistry.

Nowadays, like nearly all dentists, Gunnel Hanses uses digital X-ray technology. The photons that pass through the body are detected by a tiny sensor in the patient's mouth, held firmly in place by biting. The sensor works roughly like the photosensitive plastic film that was used formerly: the pattern of detected photons forms dark or light areas on the X-ray image.

'We've had digital X-rays for about ten years now,' Hanses says, 'and it has really revolutionised the way we work. Before, we were slowed down by needing to wait for the nurse to develop the X-ray film. Then, when it was ready after a few minutes, it sometimes turned out that not everything you wanted to see was included, or the exposure might be wrong. So you just had to take a new X-ray and wait again. Now the image comes up on the screen within a few seconds, and if something needs adjusting it can be done straightaway.'

Another advantage compared with the photosensitive film is that a much lower radiation dose for the patient is needed. The dental services also avoid problems of toxic silver from the film leaking out into drains and the use of developing fluids containing chemicals dangerous to health.

Once Gunnel Hanses has obtained an image of the jawbone, she sets to work on planning how to position the titanium implant.

'It's a bit like working in wood. We drill a hole in the jawbone and then enlarge it in several stages, using special thread taps. When we've made the hole big enough, the titanium screw can be rotated into place.'

With this description of the operation, it is easy to see how invaluable it is to be able to anaesthetise the patient. Today this is self-evident, but right up to the mid-20th century it was a question of choosing the lesser of two evils: cocaine could be used, but the risk was that patients would become addicted. There were also substances that resembled cocaine without being addictive, but they were less effective and could cause allergic reactions. It was hardly surprising that the Swedish drug xylocaine, also known as lidocaine, revolutionised dentistry. Developed in the 1940s, it provided local anaesthesia by blocking pain signals to the brain from the nerve cells.

'We still use xylocaine, since it's easy to work with. Just a few seconds after we inject it with a fine needle, the anaesthetic starts to take effect. The side-effects, too, are minimal.'

Nonetheless, there are patients who erroneously believe they are allergic to xylocaine and don't want it, Hanses explains. But this is because this substance is often used in conjunction with adrenaline, which contracts the blood vessels and prolongs the effect of the anaesthetic. Sometimes the needle hits the middle of a blood vessel and then the adrenaline can make the heart race, which is somewhat unpleasant for the patient.

Once a titanium screw is firmly fixed in the jaw, it serves as support for a crown or major bridge designed to hold several teeth in place. According to Hanses, there may be up to about a thousand different implant systems around the world. The reason is that titanium is tolerated by the body and allows bone tissue in the jaw to grow together around the screw. After a few months it has become integrated with the bone.

Gunnel Hanses remembers hearing about research on what were then the entirely new titanium implants while she was studying to become a dentist in the1970s. But for the first few years after she began working as a dentist, dentures were still the solution for anyone whose natural teeth were lost.

'Dentures are commonly known as "false teeth", after all; and false is what they are: loose, insecure and not always reliable. Getting dentures didn't give people any great quality of life — especially young patients who had lost their teeth in accidents or the like.'

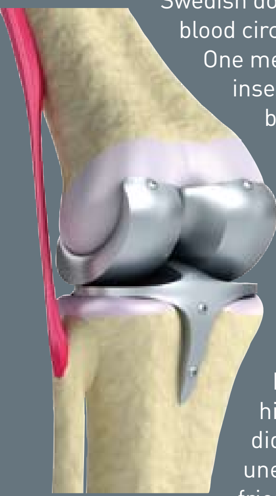
She explains that being a dentist is much more enjoyable these days. The implants inserted here at St. Erik's Hospital and other dental clinics worldwide work as well as the patients' original teeth and often last for the rest of their lives.

'In retrospect, it's immensely exciting to look back on the technological advances that have taken place in dentistry. The new tools that have come into being in the form of implants, better X-ray methods and anaesthetics mean a tremendous lot for us who work here, but above all for the patients, who can get much better care nowadays.' //

CHANCE LED TO **BODY-FRIENDLY IMPLANTS**

Today, titanium implants are used for countless purposes, from attaching new teeth and artificial fingers to repairing knee or hip joints and other worn-out parts of the body. The great value of this metal for healthcare is due to the fact that it is tolerated by the immune system, which usually identifies and rejects foreign tissue. But the research that gave rise to the various titanium 'spare parts' of our day had nothing to do with implant materials.

In the 1950s Per-Ingvar Brånemark, a Swedish doctor, carried out research on blood circulation in the bone marrow. One method he used was surgical insertion of a tiny implant chamber in rabbit forelegs. Using titanium for this purpose was largely a matter of chance, as was the fact that on one occasion it remained implanted longer than planned. By that time, the chamber had become completely integrated with the bone tissue. Brånemark was focused on his bone-marrow research, and did not realise the value of his unexpected discovery of a 'body-friendly' material until several years later. Then, however, he had difficulty in securing support for his research on titanium, since there had been discouraging experiments with many other implant materials that had resulted in painful failures. But the very first titanium implant, used when a toothless patient was given new teeth in 1965, was a success. Today, titanium implants are used all over the world and have helped millions of people with various ailments to live better lives.

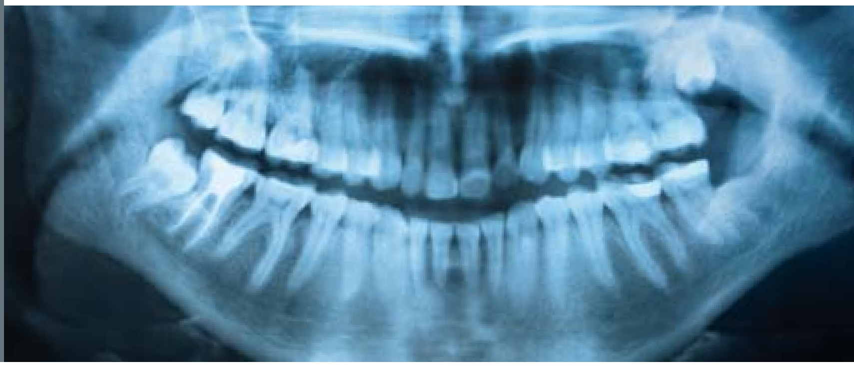


PHYSICS OF X-RAY CAPTURE

X-ray equipment spread to hospitals and dental clinics shortly after the discovery of X-rays by Wilhelm Conrad Röntgen in 1895. In this imaging technology, the energy-rich particles, photons, in the rays pass through the various body tissues and are captured on special photographic film. Today, this film has been superseded by digital sensors, which are now used in dentistry and mammography, for example. X-ray film captures only a small percentage of all photons, while the efficient sensors capture considerably more. An examination thus requires a much smaller radiation dose. The fact that there is no X-ray film to be developed also saves both time and environmental impact.

The sensors that permit present-day digital X-ray imaging are based on research that had no connection with healthcare. The technology for the most effective sensors was taken from advanced instruments built by particle physicists at the CERN laboratory in Switzerland. There, protons or other particles are accelerated and collided in the quest for the basic building blocks of matter. Ultra-sensitive sensors are used to detect the subatomic particles produced in the collisions.

Somewhat older X-ray sensors are based, instead, on CCD technology, which is also used in digital cameras. This is based on the photoelectric effect that Albert Einstein explained theoretically in the early 20th century. Much later two scientists, Willard Boyle and George Smith, attempted to build a form of computer memory in silicon based on this effect, but soon realised that what they had invented could be used to make photosensitive sensors with which digital images could be generated. In 2009, they were awarded the Nobel Prize in Physics for this discovery.



FROM TASTE TEST TO VALUABLE ANAESTHETIC

They were on the trail of a revolutionary pain reliever. But the chemists Nils Löfgren, Bengt Lundqvist and their supervisor Holger Erdtman had no idea. At Stockholm University College, the forerunner of Stockholm University, they were studying a substance found in a particular variety of barley plant with superior resistance to pests. They produced several similar substances, and one contemporary way of testing a product was, quite simply, to taste it. One of the substances proved to have an anaesthetic effect on the tongue. This is because it temporarily blocks the nerve cells so that no nerve impulses arise. After some years' development work, Löfgren and Lundqvist succeeded in creating a variant to which Astra, a small pharmaceutical company, purchased the rights in 1943. Named xylocaine (also known as lidocaine), it was a major international success. One milestone was its use in treating the Pope for chronic hiccups in the early 1950s. The revenues funded Astra's further drug development, which eventually resulted in new top-selling products, including the stomach-ulcer remedy Losec.

Göran K. Hansson himself experienced making an unexpected discovery, about the immune system's role in cardiovascular disease, which no one believed at first. He is now the Secretary General of the Royal Swedish Academy of Sciences, which has worked for 275 years to promote curiosity-driven research.

"IF NO ONE BELIEVES **in your research, you could be** on the trail of something unexpected"

When you were appointed Secretary General of the Royal Swedish Academy of Sciences, you said that the sciences' voice in public debate is more necessary than ever. Why is it important?

I am concerned about how ignorance and a disregard for facts are gaining ground in society. This applies to everything from the issues of climate change and global development to health and migration. The Academy comprises an expert panel of Sweden's foremost researchers, giving it an important role in public debate as an independent voice for science and knowledge-based development.

The Royal Swedish Academy of Sciences is engaged in several major research fellowship program in cooperation with the Knut and Alice Wallenberg Foundation and Marianne and Marcus Wallenberg Foundation. The programs gives young promising researchers the opportunity to work with bold projects with longer timeframes due to large long-term funding.

For example, we have recently taken a stand against legislation that would allow products with unproven effects to be labelled as medicines. We have also pointed out the need for new rules concerning scientific misconduct. The Academy makes regular statements about environmental and energy issues, where policies must be based on research.

Science and access to reliable knowledge are the basis of not only our economic wellbeing, but also our democracy. To contribute to this, we strive for research freedom, so the state and other research financiers do not have too narrow a viewpoint on what their investments should achieve. It may take ten years or more for a discovery to have practical applications and these could be in an entirely unexpected area.

What is the current situation for curiosity-driven research that may provide such unexpected breakthroughs?

Basic research has had fairly good conditions and, if we look at the results of Swedish research, we can only be impressed by our little country. At the same time, there are worrying signs that the state wants to provide less funding for projects that are initiated by researchers themselves, and more for major investments where the state has indicated targets. The hope is that this will lead to more innovation and new products.

There is nothing wrong with targeted research, but the Academy highlights the importance of also supporting basic research. There is actually plenty of evidence that real breakthroughs come from curiosity-driven research. If we look at how research fields and industries have developed, in many cases they are originated by people with new ideas and curiosity-driven basic research that led to new discoveries. This includes the IT industry and molecular biology businesses in Silicon Valley, as well as medical and technology companies in Sweden.

However, Swedish companies and research leaders can sometimes be slow to make the leap when it comes to new breakthroughs. For example, the key discovery leading to the revolutionary "genetic sissor", CRISPR/Cas9, was made a few years ago in Sweden. Using CRISPR/Cas9, it is now possible to make precise changes to genetic material, a kind of plastic surgery for DNA, in plants, animals, and even the human genome. The researcher who made that discovery has now left Sweden and the patents are held in other countries. Sweden needs to be better at capturing good ideas. As the world moves faster and faster, Swedish business and Swedish universities must do so too.

Göran K. Hansson is the Secretary General of the Royal Swedish Academy of Sciences and Professor of Experimental Cardiovascular Research at Karolinska Institutet.

You discovered how heart attacks and strokes are often due to inflammation caused by cholesterol in blood vessels. How was this new and unexpected knowledge, which contradicted the research of the time, received?

Previous theories had indicated that cholesterol blocked the arteries, but this didn't correspond to what we observed in samples from affected patients. On closer investigation, we instead saw that it was inflammation in the blood vessels that finally caused a blood clot, stopping the flow. But not a single person believed us at first! So, I usually tell my research students that if you believe in your data but no one else does, you could be on the trail of something new and important!

A famous example of this is the American pharmacologist Robert Furchgott, who observed that blood vessels sometimes expanded in a surprising way. This turned out to be because a gas, nitric oxide, formed in the blood vessel, making it wider. No one believed it was possible for an inorganic gas molecule to be a signalling substance in the body, but in the end Furchgott was awarded a Nobel Prize, and the applications of his discovery ranged from heart medicines to Viagra.

How can we generate the new ideas necessary for solving contemporary challenges and providing new discoveries to help us progress?

There are more people on Earth than ever before, people who need food, energy supply and many other things. This requires new solutions from future researchers. We must therefore encourage talented young people to become researchers.

In partnership with the Wallenberg Foundations, the Academy awards research grants to the very best young researchers. This gives them the chance to build up their research groups here in Sweden. We also try to influence the government, Riksdag, and university management, so that research careers are more attractive and hopefully more talented students will become researchers.

Another important task is for us to provide young people with information about research. We have started a holiday school for recent immigrants and young people from disadvantaged areas. Over one or two weeks they can meet researchers and work on interesting projects. The idea is to introduce them to the fantastic world of research and to inspire them to keep studying.

I have had an amazing journey through the world of science myself; being a scientist has given me more freedom than I would have had in any other job. My motivation is to push the boundaries of knowledge and preferably to ensure that new knowledge is of practical benefit. And when you make a new discovery, it's such an incredible feeling! Besides, I also get to work with talented and agreeable colleagues from all around the world, which means that we learn a lot about each other. //

MAGNETIC CAMERAS USED IN HEALTHCARE worldwide are based on what was initially an annoyance in basic research on atomic nuclei. The problem has now given way to a tool that provides three-dimensional images of our organs and helps doctors to identify their patients' illnesses, fast and non-invasively.

Camera born from problem facing curious nuclear physicists

New imaging technologies have revolutionised healthcare ever since the capacity of X-rays to penetrate body tissues and depict our inner organs was discovered at the end of the 19th century. Today, magnetic resonance tomography helps doctors to identify and treat many diseases. However, using this magnetic camera to investigate various organs has roots far outside medical research. The background is physicists' interest in the properties of atomic nuclei.

Nuclear physics was one of the most exciting research fields in the 1930s, and its objective was to investigate the relatively recent discovery that every atom has a positively charged nucleus. Through a range of experiments, physicists attempted to establish the structure of various elements and whether their properties show any patterns. Since atomic nuclei are surrounded by a weak magnetic field, powerful magnets became key tools in the quest for the secrets of the atomic nucleus. The nuclei can be made to align themselves with stronger external magnetic fields — roughly like tiny compass needles. One of the many nuclear physicists who worked in this area was Isidor Rabi. He succeeded in studying properties of atomic nuclei in gases by first arranging them in order with an external magnetic field and then adding energy with radio waves. The nuclei then reacted in various ways, providing valuable information about their structure. In the 1940s, two physicists, Felix Bloch and Edward M. Purcell, described how the same manoeuvre was possible for atomic nuclei in liquids and solid materials. Like their predecessor Rabi, they were awarded the Nobel Prize in Physics.

The problem was, however, that the atomic nuclei did not always retain their magnetic orientation. To avoid this disturbance, the nuclear physicists had to explore how it arose. It turned out that adjacent atoms could affect the nucleus being studied. With this knowledge, the nuclear physicists were able to minimise the disruptive elements in their surroundings and continue with their experiments.

Although the physicists' interest in this disturbance cooled after this, it started to intrigue certain chemists. They realised that they could study various substances by communicating with the component atoms using radio signals. The signal frequency and the disturbance in an atomic nucleus revealed which atoms surrounded it. By exposing an unknown molecule to magnetic fields, and capturing and analysing the radio signals, researchers were thus able to work out what the atoms were and how they were bonded to one another – something that had not been feasible before. Dubbed Nuclear Magnetic Resonance (NMR), this became an invaluable analytical tool for chemists wanting to investigate new molecules they produced.

The transformation from annoying disruption to practical benefit did not, however, stop there. Within a few decades, the field of medicine was also won. Studies of the disturbance of hydrogen atom nuclei (in water molecules, for example) made various tissues and organs distinguishable from one another because their atomic environments differ. One Swedish pioneer was Erik Odeblad, a doctor who was able to show back in the late 1950s, using magnetic resonance, that the human uterus produces a special type of secretion at the time of ovulation.

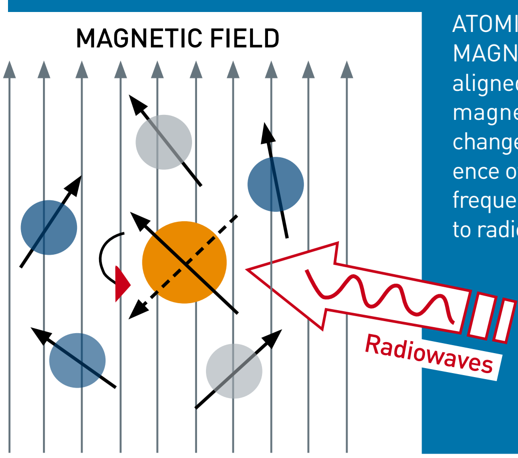
It was in the early 1970s, however, that the research groundwork was laid for breakthroughs in magnetic resonance to be made, with significant applications in healthcare. The chemist Paul Lauterbur and the physicist Peter Mansfield succeeded in producing two-dimensional images by varying the strength of the magnetic field across a tissue and subjecting the signals to mathematical calculations. The modern magnetic camera came into being and, in recognition of their work, the two scientists jointly received the Nobel Prize in Physiology or Medicine in 2003. Another physicist, Erwin Hahn, also played an important part through his study of the 'spin echo' in the 1950s. Nowadays, this is part of the technology, but at the time his manipulation of atomic nuclei had no practical benefits.

Images produced with magnetic resonance began to be used in healthcare in the early 1980s, and this technology has since been developed further. Today, it is a routinely used method capable of providing many different types of information. One major advantage of this technology is that it is not based on X-rays or any other ionising radiation capable of damaging body tissues.

Using mathematical data processing, it is now possible to construct three-dimensional images of what is being investigated and thereby show where damage is located. For example, in cancer treatment the outline of a tumour is visible, and this enables surgery and radiation treatment of patients to take place as effectively as possible, without resulting in unnecessary damage. Examinations with a magnetic camera are also superseding various interventions using laparoscopic instruments and other painful diagnostic methods.

The magnetic camera is particularly valuable for studying the brain, and not only to reveal pathological changes. By studying blood flow in the brain, using a technique often termed 'functional magnetic resonance tomography', it is possible to determine which parts are being used during various types of activity. Moving images can show how different centres in the brain are activated when the subject is exposed to various types of stimulus. This has paved the way for insights into our brains – all thanks to numerous nuclear physicists who tried to understand the inside of the atom. //

The magnetic camera is especially valuable for studying the brain. One of the first uses found for the camera was for diagnosing multiple sclerosis (MS) in patients, which had previously been difficult. Besides finding the small inflammations that give rise to the disease, it is possible to see whether they are affected by various treatments aimed at slowing down its course.

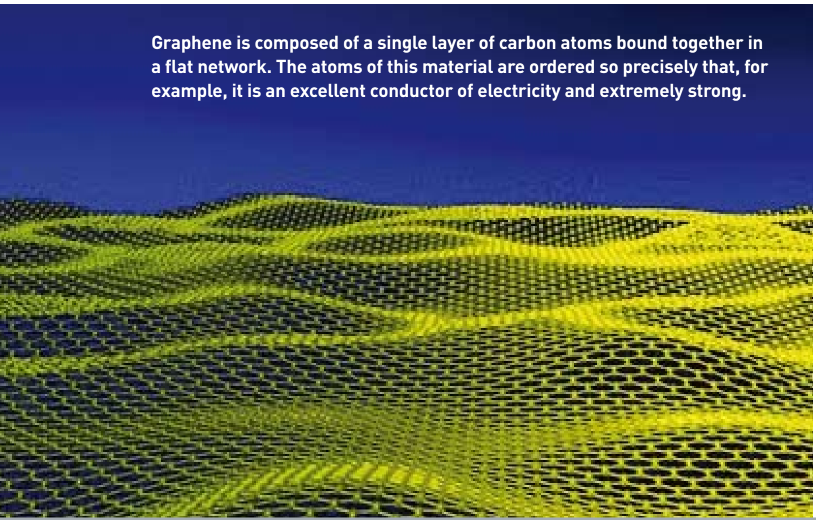


ATOMIC NUCLEI ARE WEAK MAGNETS and can be partially aligned according to an external magnetic field. They can then change direction under the influence of radiowaves of a particular frequency. How atomic nuclei react to radio signals depends on their surroundings, and this makes it possible to analyse molecules or distinguish between different tissues surrounding the nuclei.

MATERIAL OF THE FUTURE CAUGHT ON TAPE

GRAPHENE IS ONE OF THE MOST REMARKABLE MATERIALS ever studied. Its unique properties make it interesting for a wide range of applications, from new types of electronic products and solar cells to light vehicle components. Graphene conducts electricity just as well as copper, and it conducts heat better than other known materials. It is also almost completely transparent and at the same time extremely strong.

The material is a form of carbon, with the same structure as the graphite used in ordinary pencils. Graphene was discovered by chance, fortuitously and playfully, by two physicists: Andre Geim and Konstantin Novoselov. In their laboratory at the University of Manchester, they carried out tests to find out the thinnest flakes they could detach from a piece of graphite using a strip of ordinary adhesive tape. With a series of ingenious methods, they succeeded in obtaining flakes that proved to consist of a single atomic layer. Theoretically, the existence of such materials had long been discussed, but it was thought that they would be unstable and almost impossible to produce.

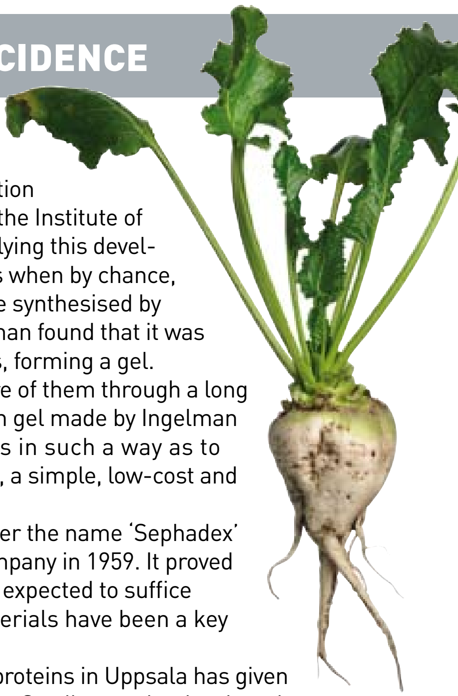


Graphene is composed of a single layer of carbon atoms bound together in a flat network. The atoms of this material are ordered so precisely that, for example, it is an excellent conductor of electricity and extremely strong.

Geim and Novoselov had nonetheless succeeded. They investigated their new material and demonstrated its various unique properties. For example, electrons move a hundred times faster in graphene than in the silicon used in modern electronics. This has paved the way for more efficient computers.

The volume of research and patents associated with this material has increased exponentially and will probably culminate in new products in a range of areas over the next few years. Despite the many possible uses of graphene, however, what underlay Geim and Novoselov's discovery — for which they were awarded the Nobel Prize in Physics in 2010 — was scientific curiosity, rather than focused materials research.

VALUABLE SEPARATION TECHNIQUE **DUE TO COINCIDENCE**



The separability of hormones, enzymes or other proteins is the basis for many enterprises in the biotechnology sector. This is feasible today thanks to the development of gel filtration by two Swedish scientists, Per Flodin and Jerker Porath, at the Institute of Biochemistry at Uppsala University in the late 1950s. Underlying this development was research on various substances in sugar beet in the 1940s when by chance, Björn Ingelman, another chemist, discovered dextran, a polysaccharide synthesised by bacteria that disrupted production at sugar mills. Unexpectedly, Ingelman found that it was possible to cross-link this substance to generate a matrix of molecules, forming a gel.

Porath and Flodin worked on isolating proteins by pouring a mixture of them through a long glass tube filled with starch. Instead, by chance, they tested the dextran gel made by Ingelman a decade earlier. Surprisingly, the matrix in the gel divided proteins in such a way as to separate them by size, thus enabling each of them to be isolated. Thus, a simple, low-cost and unique method of separating and purifying biomolecules was born.

This method, also known as 'molecular sieving', was launched under the name 'Sephadex' (Separation Pharmacia Dextran) by the Pharmacia Fine Chemicals company in 1959. It proved a huge sales success. A consignment of Sephadex shipped to the USA, expected to suffice for the first year, was gone within a week. Since then, various gel materials have been a key business area for Pharmacia and this company's successors.

Over the past century, basic research in technology for separating proteins in Uppsala has given rise to key applications and commercial successes. Professor Theodor Svedberg, who developed the ultracentrifuge in cooperation with several industrial enterprises, was awarded the Nobel Prize in Chemistry in 1926. His pupil Arne Tiselius received the same prize in 1948 for developing adsorption chromatography and protein analysis by means of electrophoresis.

BRILLIANT METHOD FOR DECODING DNA WITH LIGHT SIGNALS

In modern biotechnology, knowledge is based on our ability to analyse information contained in genetic code. This information is provided by the order of the four different building blocks known as 'nitrogen bases' in the long DNA molecule. Today, of the three methods used to determine the sequence of these bases, the fastest arose from an unexpected sidetrack from Swedish basic research.

At Stockholm University in the mid-1980s, the biochemist Pål Nyrén carried out research on what controls the transfer of energy in certain bacteria. Out of this work, he developed a method of generating tiny light reactions, which could be followed in detail, for every energy transfer.

A few years later, cycling home from the laboratory one day, Nyrén realised that the method could be used to map DNA sequences. With 'pyrosequencing', as the technique he developed is called, it is possible to follow which of the four nitrogen bases, in turn, bind to an unknown DNA fragment, since they then emit the light signal that Nyrén had studied previously. Ultimately, following the series of light signals makes the whole code of the DNA fragment obtainable.

Pål Nyrén refined pyrosequencing at KTH Royal Institute of Technology in Stockholm, and the method is now used all over the world. It has contributed to the extremely rapid development of DNA sequencing. Soon it will be possible to analyse an individual's entire genome in one day for just a few hundred dollars. Compare this with the first mapping of the three billion nitrogen bases in human DNA, which took more than ten years and cost several billion dollars.

Contributions made by pyrosequencing include its impact on views of human development. Svante Pääbo, a Swedish scientist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, has used the technology to survey large portions of the Neanderthal genome.

FRAGRANT SIGNALS **PROTECT AGAINST INSECT PESTS**

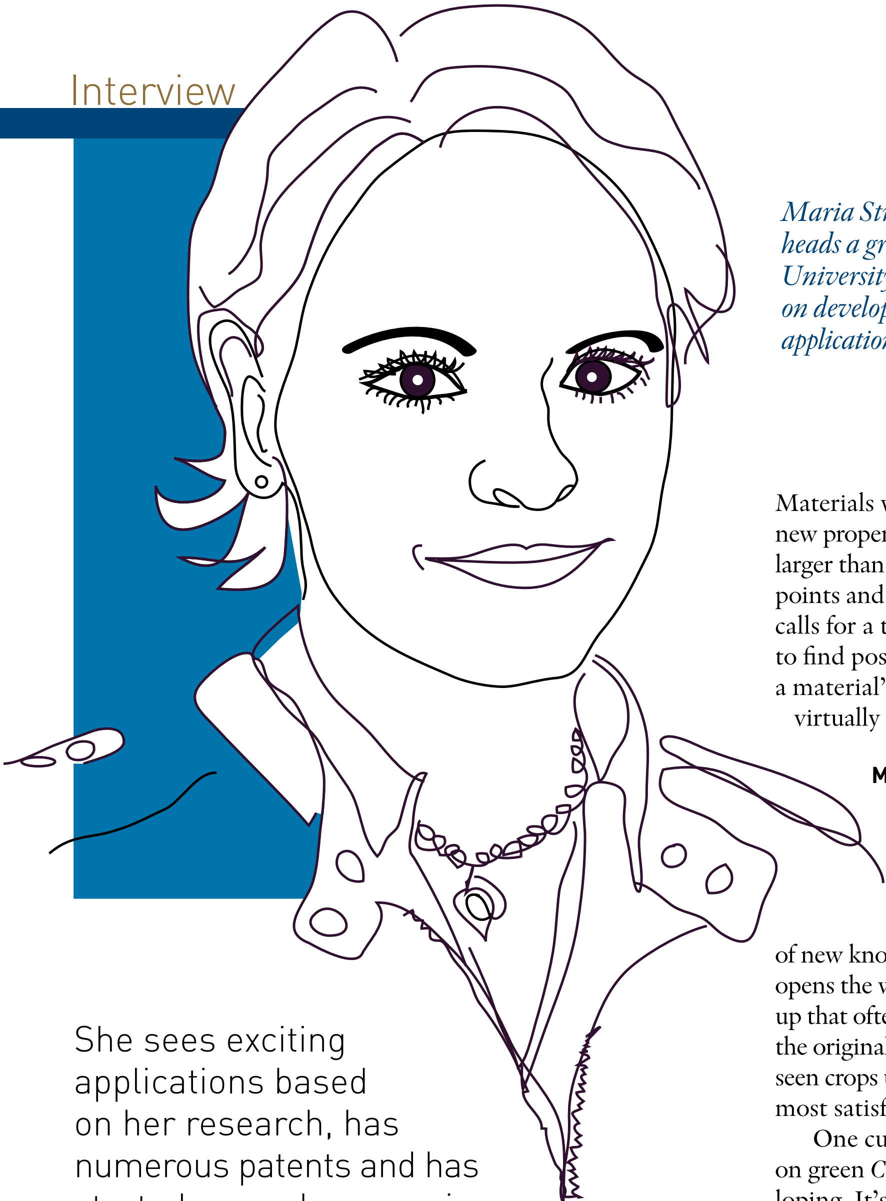
INSECTS RELY ON CHEMICAL SCENT SIGNALS to find potential partners. With their sensitive olfactory antennae, they also sniff for scents from plants and other food. For more than a century, scientists have had an inkling of the fact that insects can communicate in a way that works across long distances. However, the chemist Adolf Butenandt was the first person to show that this takes place by means of specific scent substances.

In 1959, after two decades' research, Butenandt succeeded in isolating bombykol, the substance secreted by female silk moths to attract males. The male moths are inconceivably sensitive to this olfactory signal, reacting to a concentration corresponding to the number of sugar molecules in a drop of water from a lake in which one lump of sugar has been dissolved. Butenandt obtained the few milligrams of the substance he needed in his research thanks to devoted employees who cut the scent-producing glands out of half a million farmed female silk moths.

Two other chemists gave the name 'pheromones' to scent substances that are picked up by individuals of the same species. In the following decades, hundreds of these chemicals were identified in other insects, and scent substances used for communication between different species in the animal and plant kingdoms were discovered as well. Here, the Swedish biologist Bertil Kullenberg was a pioneer, leading research that showed that a flower called Fly Orchid emits the scent of a female wasp to attract and get pollinated by male wasps.

Interdisciplinary collaboration between biologists and chemists and development of sensitive analytical methods and processes to make scent substances on a larger scale are now teaching us more and more about using olfactory signals to combat insect pests. This method can replace methods with more environmental impact. Today, scent substances are used to confuse or trap insects that are detrimental to everything from maize and fruit to cotton plants and trees. The hope is that control of insects that spread dangerous diseases will also become feasible. One advantage of these substances is that their messages are highly specific, and often limited to single species. Accordingly, such measures do not affect other insects.

Basic knowledge about the scent signals of the silk moth paved the way for a whole array of chemical attractants for controlling insect pests in crop cultivation and forestry. In Sweden pheromones are used in apple orchards, for example, and to reduce the very costly pest attacks on spruce trees by the spruce bark beetle.



Maria Strømme, Professor of Nanotechnology, heads a group of some 20 researchers at Uppsala University. The main focus of their research is on developing nanomaterials and methods with applications in the life sciences and energy storage.

She sees exciting applications based on her research, has numerous patents and has started several companies. But **MARIA STRØMME**, a nanoscientist, sings the praises of freely pursuing knowledge of basic phenomena. The result is that benefits frequenztly crop up in unexpected sidetracks. Her sustainable algal cellulose battery, which has created a worldwide stir, is the latest example of this.

Your research on nanoscale properties of materials has yielded several promising areas of application. What role has basic research played in your results?

When I start a project, being able to see a planned benefit of the research is important to me. But once we've got going and are beginning to seek understanding of various phenomena in materials science, we have to go down to an extremely basic level.

Materials with nanostructures have completely new properties, since their surface area is often far larger than materials in bulk form. Their melting points and electrical properties both change. This calls for a totally different way of thinking, and to find possible uses, we first have to establish a material's basic properties. In fact, we devote virtually all our time to basic research.

Many good ideas often emerge as sidetracks in the course of other research, and this seems to apply to your research group as well. Why is this?

Our research on fundamental scientific problems gives us a platform of new knowledge about various materials. This opens the way for unexpected sidetracks turning up that often prove to be at least as interesting as the original project idea. When something unforeseen crops up in the research like this, those are the most satisfying days you can have on the job.

One current example is the battery based on green *Cladophora* algae that we're now developing. It's quick to charge and composed of renewable raw materials. For more than ten years, we'd carried out research on basic material properties of the cellulose in this alga, as a drug carrier, for example. The cellulose interacted with water in a way that led to our discovery that it could easily be covered with a thin layer of a conductive polymer, to trap huge numbers of charged ions. This meant that it was an interesting substrate material for a battery electrode.

How did you yourself discover that what may be seen as 'useless' basic research may have key applications?

I'm basically a physicist and did my PhD in the area of solid state physics, in which I studied ion transport across interfaces in materials and how the surface affected this transport. The trigger was my pursuit of a basic understanding of what was happening, with no thought of any possible applications. But they turned out to exist. By chance, I met a drug researcher who needed help in developing a method

Nanoscientist who sees benefits IN SIDETRACKS FROM BASIC RESEARCH

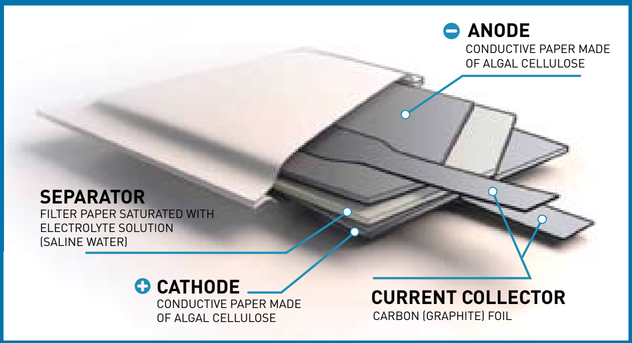
to solve a specific problem relating to the release of drugs. It proved that this could be solved with the knowledge I had of ion transport. This made me realise how valuable basic physics and materials science can be in the life sciences, which has become my present research area.

Another example of a sidetrack is our research on materials for implants designed to deliver antibiotics, to prevent infections. In this research, we've now embarked on finding out how the actual implant material can become antibacterial instead, by being given a surface that is both bioactive and photocatalytic, and can thereby kill bacteria.

Increasingly often, we hear people expressing the wish that research initiatives should provide benefits. Based on your experience, how can research be as beneficial as possible?

Taking too narrow a view of what kinds of answers research should give isn't a good idea. Many exciting applications turn up, as I said, in sidetracks of science that provides basic knowledge. I'd like to carry out more research in which I can investigate unexpected discoveries of this kind — what's known as 'serendipity' in the research community. But today it's difficult to get research funding that allows this because, right from the start of a project, funders want a clear plan with interim and final targets. And they want to know how the project is relevant in the form of benefits to society or how it will fit into existing knowledge. These demands make it difficult to deviate from the original project plan.

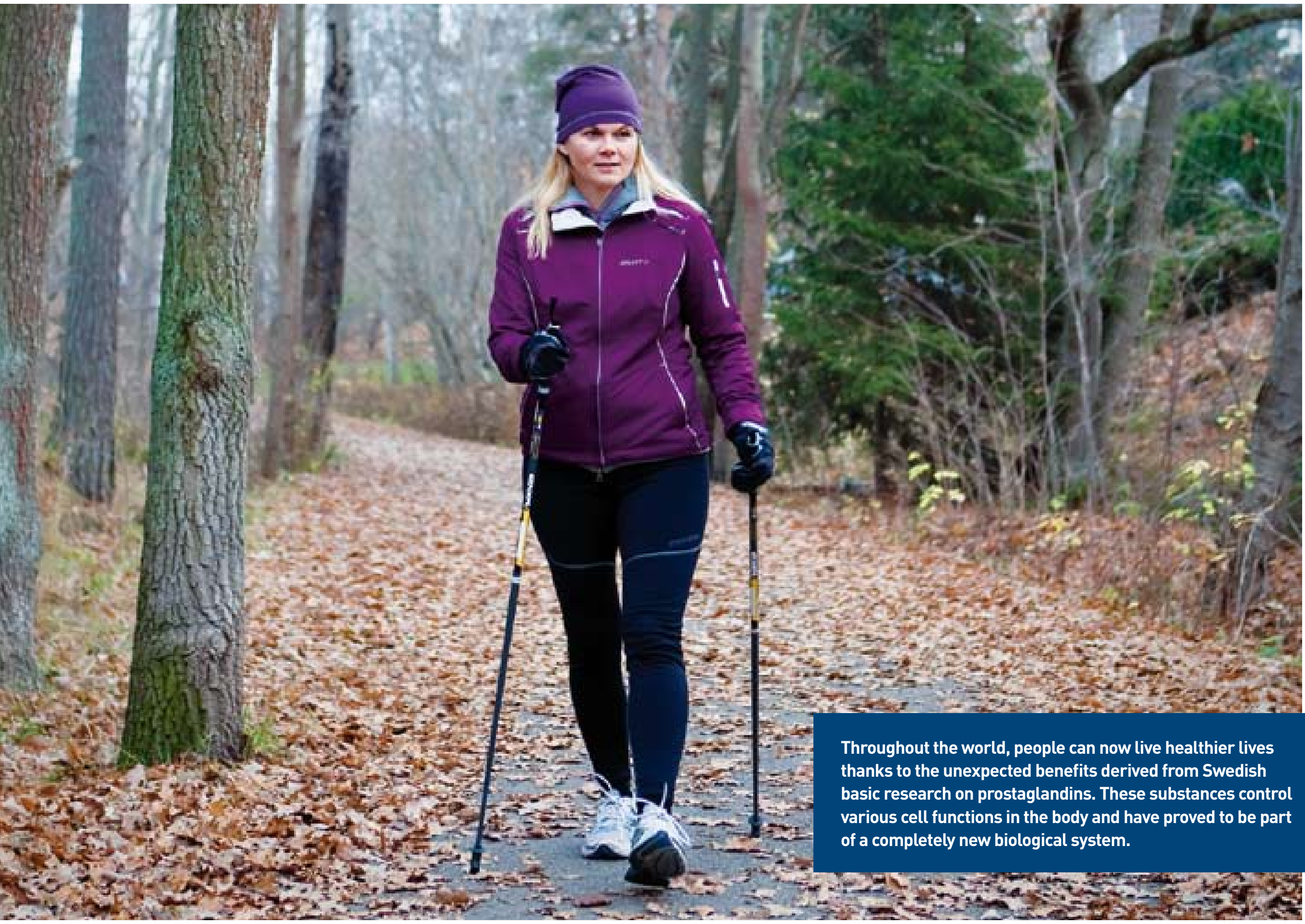
It might be good to have more initiatives focusing on people instead. If you've shown yourself to be a good researcher, it should be possible to apply for non-earmarked funds that you're allowed to use as you see fit. That would result in very exciting research. For me, it's possible to follow new sidetracks before these have matured enough to become the basis of new research applications, thanks to funds from the University that I've secured and can use more freely. I've also been awarded personal grants from the Royal Swedish Academy of Sciences and the Swedish Foundation for Strategic Research that have been extremely valuable and helped me to build up the platform I have today. //



A SCIENTIFIC ARTICLE ABOUT A BATTERY WITH ELECTRODES made of algal cellulose created a huge stir and was reported in the news all over the world. The green filamentous alga, in the genus known as *Cladophora*, abounds in the Baltic Sea and elsewhere. The first battery prototype was charged in 10 seconds, and the Motorola company is now collaborating with Maria Strømme's group to develop a 'green' rechargeable remote control based on the algal battery.

IT ALL STARTED WITH AN UNEXPECTED OBSERVATION *that led to the discovery of a whole family of substances in the human body that regulate our cells. Swedish research in this area has resulted in both scientific honours and tremendous benefits in work to combat various diseases. This knowledge has yielded drugs that help millions of people, for example with cardiac problems, glaucoma, asthma and pain.*

NOBEL PRIZE-WINNING **biological system that improves our health**



Throughout the world, people can now live healthier lives thanks to the unexpected benefits derived from Swedish basic research on prostaglandins. These substances control various cell functions in the body and have proved to be part of a completely new biological system.

Exciting new discoveries about prostaglandins are still being made, although research on these substances began back in the 1930s. Ulf von Euler, a physiologist, observed that there was something in semen that resulted in reduced blood pressure and contraction of muscle tissue in the uterus and elsewhere. He called the unknown substance prostaglandin, since he believed that it was formed in the prostate gland. This finding has led to the discovery of a whole family of substances that affect cell functions.

A young biochemist, Sune Bergström, met von Euler at Karolinska Institute some years later and became curious about his initial discovery. In due course, he isolated various substances from samples and determined their structure, in cooperation with his colleagues Bengt Samuelsson, Ragnar Ryhage and Jan Sjövall. In the early 1960s, thanks partly to the emergence of new analytical methods, they were able to present the structure of six different prostaglandins.

This made it possible to devise methods of producing them on a large scale in the laboratory, instead of extracting them from seminal vesicles and elsewhere. The research then attracted industrial interest and, in the 1970s, pharmaceutical companies distributed prostaglandins to doctors for clinical trials. The medical effects of these substances were investigated in controlled ways, and these helped the researchers to discover a great array of different biological functions. Prostaglandins proved to regulate and balance many of the body's functions at cell level, and they began to be used for such purposes as relief of stomach-ulcer problems, induction of labour in childbirth and treatment of glaucoma. Prostaglandins are also active in inflammations and are therefore targeted by many analgesics that block formation of these substances, thereby relieving pain and other symptoms.

Once the structures were known, Bengt Samuelsson was also able to show how prostaglandins are formed from essential fatty acids, especially arachidonic acid. This enabled him, with his colleagues, to investigate and isolate new substances resembling prostaglandins, including thromboxane, which is formed in blood platelets. This substance stops bleeding, but also contributes to the formation of blood clots that may cause stroke and heart attacks. This discovery has led to the development of a low-dose variant of aspirin that millions of people worldwide take to reduce the risk of clots in the heart and brain.

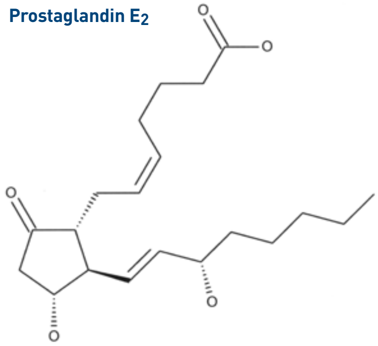
Another drug that relieves asthma is based on a further stage of Bengt Samuelsson's exploration of the family trees of substances. In the late 1970s, he suspected the existence of an unknown group of substances related to prostaglandins, and succeeded in isolating a few potential candidates, formed in white blood cells. During a sailing trip in the Stockholm archipelago, he suddenly realised that these might be the preliminary stages of a substance he had heard of that triggered asthma. Allergy researchers had dedicated decades to attempting to identify it, but within just a few months, Samuelsson and his colleagues succeeded in showing that their theory was correct.

The new substances, given the name of leukotrienes, inspired such high hopes that, immediately after Samuelsson presented the discovery at a scientific conference in Washington, DC, in 1979, drug companies started developing new drugs to treat asthma. One lesson is that the solution did not emerge from focused research aimed at understanding, for example, allergic reactions. Instead, it arose from fundamental understanding of biochemical mechanisms due to discoveries made without any specific clinical benefit in view.

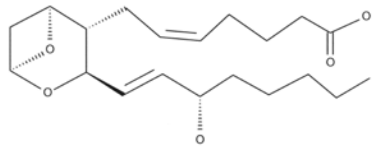
Sune Bergström and Bengt Samuelsson were awarded the Nobel Prize in Physiology or Medicine in 1982, jointly with the British scientist John Vane, who had carried out research on aspirin. But exploration of this field is far from complete. It looks as if, for example, new discoveries can yield analgesics with smaller side-effects and drugs to combat arteriosclerosis. //

THE SUBSTANCES DEPICTED ARE INCLUDED IN THE LARGE FAMILY of prostaglandins, thromboxanes and leukotrienes that were discovered and surveyed in the course of basic research with no planned clinical benefit. The researchers were driven by their desire to determine the structure of these substances and how they are formed in the body, without knowing that their work would give rise to numerous drugs. Some examples of these are Trombyl (a blood-thinning medicine), Cytotec (treatment of stomach ulcers), Celebra (an anti-inflammatory agent), Minprostin (induction of labour), Prostivas (emergency treatment of newborns with congenital heart defects), Xalatan (treatment of glaucoma), Singulair (asthma treatment) and Ventavis (treatment of impaired lung function).

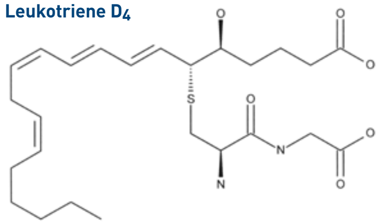
Prostaglandin E_2



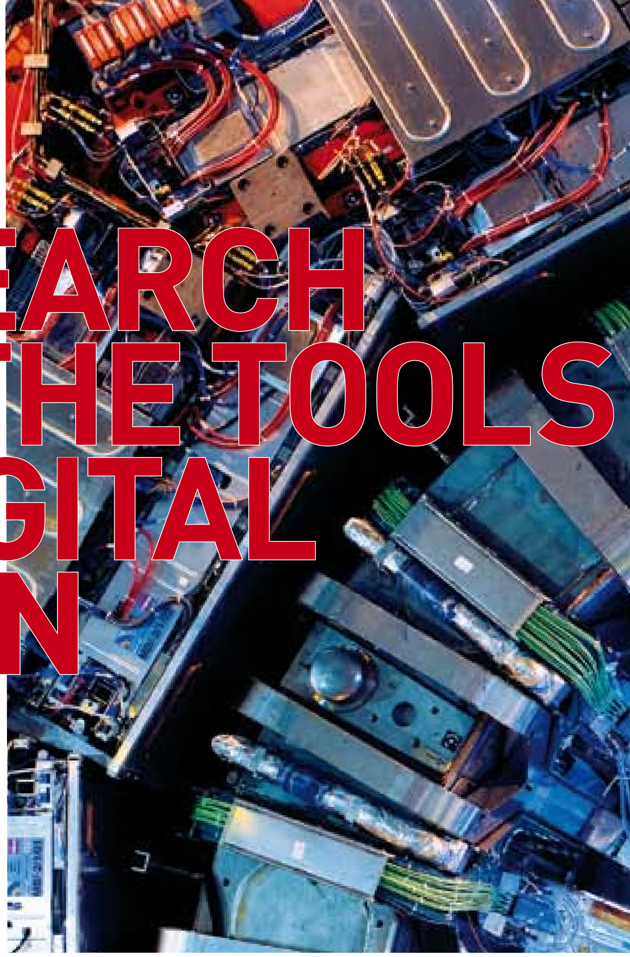
Thromboxane A_2



Leukotriene D_4



BASIC RESEARCH PROVIDED THE TOOLS FOR THE DIGITAL REVOLUTION



Smart telephones and computers are part of our everyday life. The screen in front of us may be a global news agency or a digital way of relaxing with our friends, an efficient work tool or an enormous library that provides every conceivable form of entertainment. All these functions, which are taken for granted nowadays, are based on our ability to communicate rapidly, easily and securely on the Internet.

'Today, millions of Swedes listen to music on Spotify, buy things online, are active on Facebook, play online games and watch web TV. The most recent sector to change as a result of IT development is the film industry, now that we're beginning to watch films on our computers more and more,' explains Peter Alvarsson, one of the many new entrepreneurs who have perceived the potential of digital technology.

When Alvarsson began offering films on the Internet five years ago, he belonged to the wave of new entrepreneurs with ideas about how it could be used for business and to provide information and entertainment on a commercial basis. Evidence that Sweden is well ahead in the digital labour market includes the fact that in the past few years, despite the global financial crisis, the Swedish IT industry has grown by 25% in terms of turnover and workforce alike.

The ability of people and businesses around the world to exchange information, shop securely and generate job opportunities in occupations that did not even exist a few years ago is largely due to a series of scientific discoveries. These came from physicists and chemists researching the tiniest components of matter and the energy levels of atoms, as well as from mathematicians who demonstrated elegant calculations long before computers had been invented.

For example, the fact that we can find our way around all the innumerable websites on the Internet, containing altogether an estimated 1,000 billion unique pages, is an example of the unexpected benefits of major projects in particle physics at the CERN laboratory in Switzerland. The physics researchers' need to be able to work together prompted the idea of connecting digital documents together with links to a network that would make it easy to find one's way to the right information. Because this technology was so successful, it spread outside the research community and gave us the vast World Wide Web, binding together all digital information today.

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Today, everything is accessible — everywhere, all the time. News, entertainment and contacts with friends and colleagues around the world are just a few clicks away. We can communicate and do business online, thanks to basic research in physics and mathematics that resulted in a range of discoveries that, in turn, became the basis of today's wired society.

The CMS detector is one of the advanced experiments at CERN, where the World Wide Web was born as a research tool in particle physics.

Optical fibres have immensely larger capacity than ordinary copper wires and are the backbone of our digital infrastructure.

At the office of Headweb, a company run by Peter Alvarsson, he accesses the company's website on his computer to show how one can search the range of films and TV series on offer to rent and watch online. Like many services on the Web today, the idea is based on streaming technology. This means that there is no need for customers to wait for films, music or any other data files to be downloaded: instead, we can start watching or listening on our computers straightaway.

'From being a fairly sluggish market, online film rental has now become a fast mover. By 2013, according to assessments, we'll buy or rent more film online in the Nordic region than on DVD,' Alvarsson says.

The fact that we dare to send credit-card details when paying for films and other purchases at various websites is also based on fundamental scientific discoveries. With the latest security technology, our own and the bank's computers encrypt the information exchanged to prevent any outsider from reading the sensitive data. This transaction, taking a mere second, is based on mathematics worked out several hundred years ago, when couriers on horseback were the fastest and most reliable means of communication – long before anyone could have foreseen that such calculations would be crucial components in the present-day digital revolution.

One effect of our new habits of watching films, speaking on the phone and listening to music online is the rapid expansion of digital traffic. The basis for ever more people's access to the new services is that large volumes of data can be transmitted between computers, and this, in turn, is based on fundamental physics research on laser light. All the optical fibres that are the motorways of the IT society use extremely rapid laser pulses, transmitted along thin glass threads. The transmitter converts the ones and zeros of computers into pulsating light that rapidly reaches a recipient at the other end of the fibre, many miles away, where the light pulses are converted back again and are usable by another computer.

'Optical fibres have immensely larger capacity than ordinary copper wires, and are the backbone of our digital infrastructure. The fact that Sweden today is well to the fore in IT is thanks to central government initiatives that got everyone buying subsidised home computers and telecom operators laying underground fibre cables in large parts of the country,' Alvarsson says.

The Swedish government has adopted the target of Sweden being best in the world at using the potential of digitisation. The reason is that IT development offers new solutions in the form of, for example, telemedicine in healthcare, smart energy regulation of electricity grids and wired vehicles for safer, more efficient transport. Other examples of the benefits of the Web are the recent democratic revolutions around the world, where many commentators stressed the importance of activists being able to spread their message online.

For all this, we have scientists with inquiring minds to thank – researchers who, without knowing it, paved the way for today's wealth of technology that continues to enrich our everyday lives. //

BRILLIANT APPLICATIONS

Extremely high power and precise frequency are examples of properties that light can take on in a laser. Besides transmitting data in optical fibres, the technique is used for everything from cutting and welding steel to carrying out surgical operations with high precision. Laser light can also be used to detect cancer, measure air pollution, study chemical reactions, or read and burn CDs and DVDs.

The American physicist Theodore Maiman constructed the first laser in 1960. The word is an acronym of 'Light Amplification by Stimulated Emission of Radiation', and the technology is based partly on research carried out in the 1950s by Charles H. Townes, Nikolay Basov and Aleksandr Prokhorov, who were awarded the Nobel Prize in Physics in 1964.

However, no one foresaw that it would be possible to use this technology for any useful purpose. Instead, the research was driven by curiosity about the physical phenomenon of stimulated emission, which Albert Einstein had theorised about back in 1917. The basic principle is that atoms excited to a higher energy level can be steered so that they emit energy in the form of light in a highly controlled way. Today, the 'useless' laser has become an invaluable tool in various research fields and has yielded numerous everyday applications.

ANCIENT MATHEMATICS AND PRIME NUMBERS FOR SECURE TRANSACTIONS

Encryption is used by the world's banks to move vast sums online every day. It is based on number theory, developed by two mathematicians: Euclid and Pierre de Fermat, 2,000 and 400 years ago respectively. Their maths was available when present-day computer communication generated the need to be able to send sensitive data easily without anyone eavesdropping. Classic encryption is based on transmitters and receivers having the same encryption key to code and decode a message. This would be hard to organise for the billions of Web users today.

The solution was RSA encryption, named after the surnames of its developers Ronald Rivest, Adi Shamir and Leonard Adleman. Nowadays, the technique is used on secure pages where the URL begins with 'https://', and the refinement is that every computer has an open, externally visible key as well as a secret, private one. The computer that transmits information uses the recipient's open key to encrypt the message, while the receiving computer then uses its private key to decrypt the information.

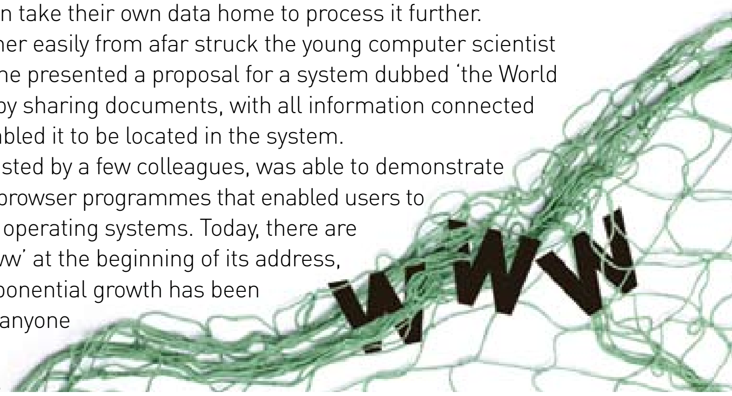
The keys are two very large numbers that the computer generates by first multiplying two large prime numbers, i.e. numbers divisible only by 1 and themselves. It is impossible to decrypt a message without knowing what these two prime numbers are, so only the recipient computer knows. The calculations underlying RSA encryption are based on Euclid's Extended Algorithm and Fermat's Little Theorem.

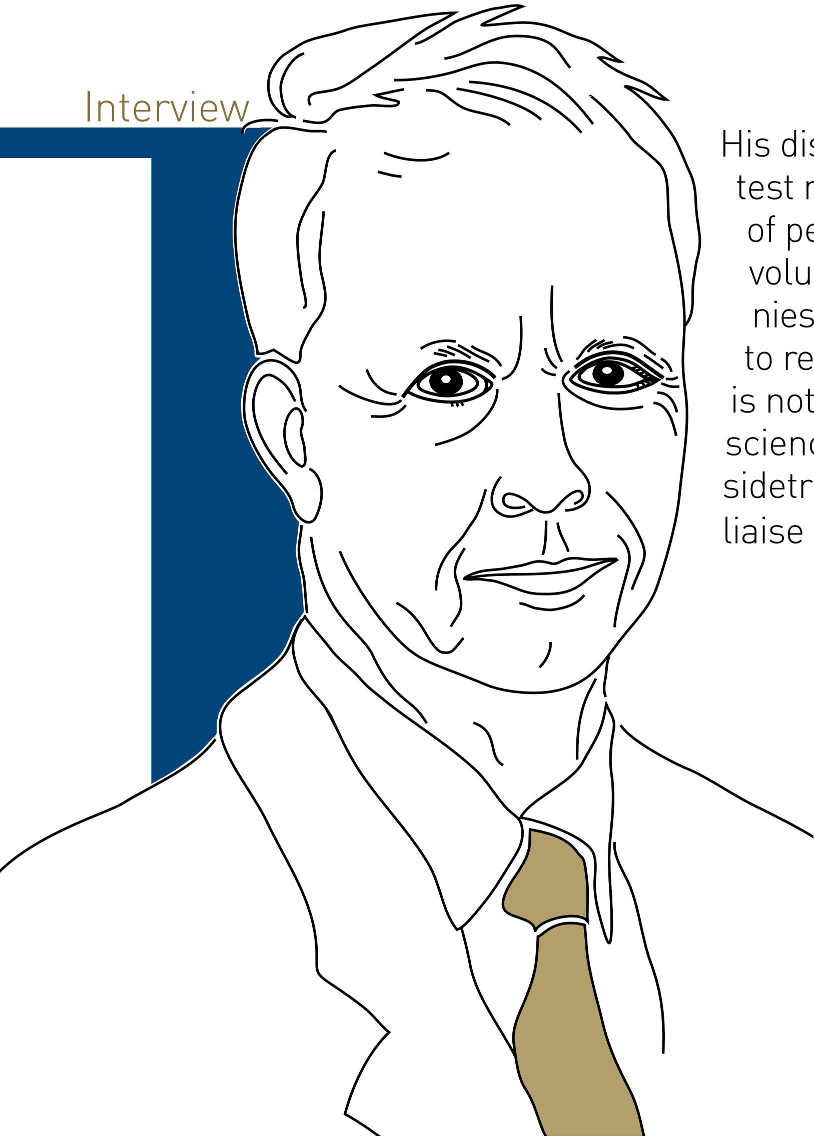
2,3,5,7,11,13,17,19,
23,29,31,37,41,43...

PHYSICISTS WHO **CAPTURED THE WEB**

We owe our ability to surf on the Internet to research that took place at the CERN laboratory near Geneva. There, a large number of research groups are working in particle physics on vast quantities of data from various accelerator experiments. Many researchers are on the site for short periods only, and then take their own data home to process it further. The importance of being able to communicate and work together easily from afar struck the young computer scientist Tim Berners-Lee, who worked at CERN in the 1980s. In 1989, he presented a proposal for a system dubbed 'the World Wide Web' that would allow researchers to collaborate online by sharing documents, with all information connected by 'hyperlinks'. Every document had a unique address that enabled it to be located in the system.

Berners-Lee received funding to develop the idea and, assisted by a few colleagues, was able to demonstrate the first website at CERN in August 1991. Soon there were web browser programmes that enabled users to read hypertext documents irrespective of their computers and operating systems. Today, there are hundreds of millions of websites, each still with the letters 'www' at the beginning of its address, to commemorate Berners-Lee's name for the project. This exponential growth has been due both to the simplicity of the technology, which means that anyone can explore the Web without special prior knowledge, and to the fact that CERN released the technology with full public access.





His discovery made it possible to develop test methods that have helped millions of people with allergies and led to high-volume products for Swedish companies. The recipe for success, according to researcher **GUNNAR JOHANSSON**, is not focused research but open-ended science that is free to pursue interesting sidetracks and where researchers can liaise informally with the business sector.

Gunnar Johansson is Professor of Clinical Immunology at Karolinska Institute and, since the discovery of the antibodies that set off allergic reactions in the body, has devoted most of his time to allergy research.

You and your colleague's discovery of a new class of antibodies has resulted in effective modern allergy testing. But were there any such plans for the research from the start?

Not at all. It started when, as a medical student, I got an extra job at the blood bank at Uppsala University Hospital. There was an interest in purifying proteins in blood serum, and we set up a laboratory for it in the early 1960s in cooperation with Hans Bennich at the Department of Biochemistry. Immunoglobulins had been found in blood. These are proteins that become the basis of various antibodies and help the immune system to identify foreign substances. The research interest was in learning more about their basic properties, with no thought of specific applications.

We purified proteins from patients, and one day there suddenly cropped up in a sample a variant that did not behave like the known immunoglobulins. Hans Bennich and I investigated this finding further, and soon realised that it had a unique structure and set of immunological characteristics. It represented an entirely new class of immunoglobulins and was named 'IgE'. Our finding would later revolutionise research on allergies and solve an enigma observed by a doctor, Maximilian Ramirez, back in 1919. One of his patients suffered an allergic reaction to horses after a blood transfusion. Ramirez discovered that the blood donor had asthma and the trigger of this reaction must be something transferred in the blood — which we showed to be IgE.

Is there any connection with the fact that the discovery was made in Uppsala, where many other research-based products in medical technology and pharmaceuticals have come into being and given rise to several companies?

Ever since the 1930s, when Nobel Laureates Theodor Svedberg and Arne Tiselius made their discoveries in protein research, Uppsala has been an environment that has encouraged further investigation if anything unexpected cropped up in the basic research. This has yielded a series of scientific discoveries that have been developed into various products. One key aspect is that it has been easy for the scientists and companies to get in touch. There has long been a positive environment that has made it easy to meet and discuss possible applications. In the allergy research group I later established, for example, we had weekly meetings. Former colleagues who had started working at various companies also attended, and contributed ideas.

What was it like in your case, the journey from research findings about IgE to a successful product?

When we'd managed to isolate and determine the structure of the new immunoglobulin, the quest

DISCOVERY **at the blood bank gave huge** REVENUES

to find IgE in more people started. We examined blood samples from hundreds of blood donors, and surprisingly enough one sample contained concentrations many times higher than the others. Our closeness to clinical work was then valuable. We contacted the donor, who was completely healthy except that she proved to have allergic asthma. This prompted us to examine samples from other asthmatics — and the connection then became crystal-clear. IgE was present in elevated concentrations in almost all the samples.

As I said, there were longstanding contacts between the academic community and local businesses in Uppsala. We contacted Leif Wide at Uppsala University Hospital, who had experience from developing a sensitive hormone test. Jointly with the company Pharmacia, we developed an allergy test that was able to show and measure IgE antibodies in blood samples from people with allergies. The alternative, which was used by allergologists, was skin prick tests, which are still highly unreliable today. Our test, known as RAST, was launched in 1974, and when we measured the quantity of specific antibodies, it showed whether the person was allergic and, if so, against what. Today, various versions of the tests are used worldwide and they have brought in vast sums for Pharmacia Diagnostics and that company's successors.

Based on your experience, what is needed in the present-day research climate for us to make new discoveries that can develop into successful products?

The challenge is that it's difficult to know in advance what will be valuable. Our research, for example, illustrates this. When we applied for funding in the late 1960s, so that we could go on investigating our new immunoglobulin, we were denied grants from the Swedish Medical Research Council. Later, we learnt that one of the leading scientists there had judged the discovery as being entirely uninteresting.

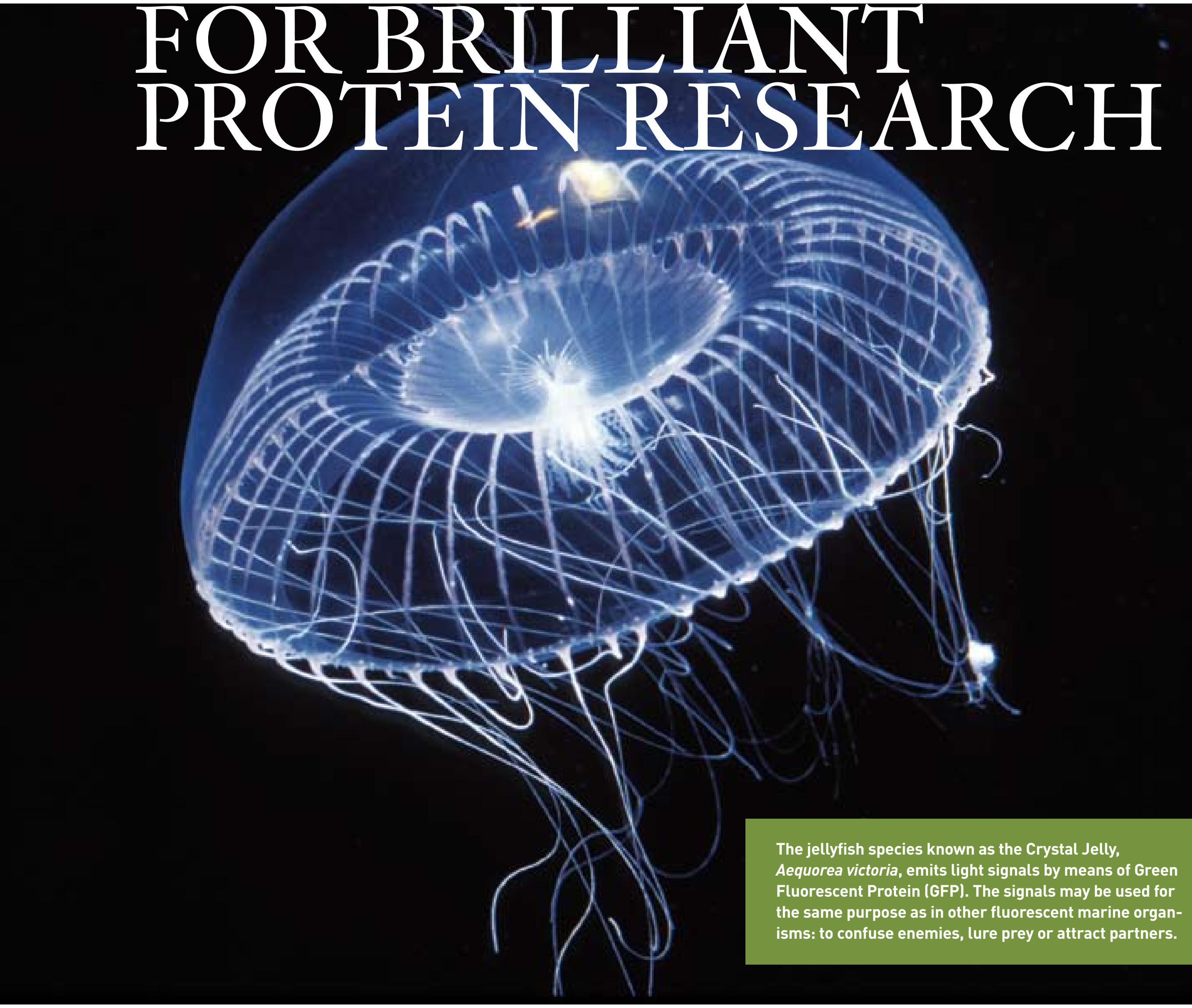
Basic research of high quality can often yield valuable applications in the long term if, like our research on antibodies, it provides knowledge of fundamental phenomena. But it mustn't be too tightly controlled. Many funders' idea of research today is that it should take you to a point that is defined in advance. With this view, we don't get researchers who are observant when it comes to unexpected discoveries and who sit up and take notice when an interesting scientific sidetrack crops up. And these sidetracks, as in our case, may often bring the most important applications. //

A BLOOD TEST can provide a quick answer as to whether you are allergic to something. This simple allergy test, which can be done at the pharmacy, measures the concentration of various IgE antibodies against specific pollen and animals. Like 70% of all allergy tests carried out at laboratories in the world, it is based on the basic research in Sweden on immunoglobulins in the blood.

Leif Wide, Hans Bennich and Gunnar Johansson in 1974, when their allergy test was launched.

ALMOST EVERYTHING THAT HAPPENS IN A CELL is controlled and carried out by various proteins. An ability to study where and how all these proteins are active is invaluable for an understanding of how the human body works and how different diseases develop. Nonetheless, one of the most valuable tools for these particular studies is not the outcome of large-scale initiatives in biochemistry and medicine. Instead, it is based on basic research on bioluminescent jellyfish.

JELLYFISH GAVE GREEN LIGHT FOR BRILLIANT PROTEIN RESEARCH



The jellyfish species known as the Crystal Jelly, *Aequorea victoria*, emits light signals by means of Green Fluorescent Protein (GFP). The signals may be used for the same purpose as in other fluorescent marine organisms: to confuse enemies, lure prey or attract partners.

Today, we can monitor cell processes in order to understand how various organs form and then function. It is also possible to see in detail how cancerous tumours spread or how other diseases destroy vital tissues in the body. These advances have been feasible thanks to a tiny fluorescent protein that can be used to tag other proteins a researcher wishes to study. Light signals are emitted by the tags that localise the proteins in a cell or organ, and reveal which other proteins they interact with.

BY MAKING NERVE CELLS PRODUCE GREEN FLUORESCENT PROTEIN (GFP), Martin Chalfie was able to follow exactly how the nervous system developed in the species of transparent worm he was studying. When Chalfie published his results in ***Science*** in 1994, the photograph showing the worm's luminous green nerve cells was on the cover.

What happens in a cell is controlled by tens of thousands of different proteins with various functions. By using light to mark the activities of selected proteins, it is possible to monitor different processes in an ordinary microscope. Previously, scientists had to add various reagents that bond with the right proteins in a cell or organ and, for example, to dye them in order to show whether they were present in samples and, if so, where. This called for a great deal of work and sometimes proved impossible. Moreover, one major disadvantage was that this procedure yielded only still images and did not register the dynamic nature of living tissue.

Using the green light for tracking proteins, researchers can obtain new knowledge of cells of various types. This improves the prospects of identifying various diseases at an early stage and developing drugs to combat them without troublesome side-effects.

The present-day existence of such a brilliant tool is due to the Japanese marine biologist and chemist Osamu Shimomura. At Nagoya University in the 1950s, he studied fluorescent marine organisms to understand what gave them their luminescence. After a few years, Shimomura took his research and moved to Princeton University, where he began studying the Crystal Jelly, *Aequorea victoria.* For one whole summer, Shimomura collected thousands of jellyfish on the American West Coast. His research was driven by curiosity and interest, with no thought of any applications, but resulted in benefits of huge practical significance.

Shimomura showed that the outer edge of the jellyfish sometimes glows green because it contains a protein that absorbs blue or ultraviolet (UV) light and converts it into green light. The isolated protein was named 'Green Fluorescent Protein' (GFP).

Twenty-five years passed before the next step was taken towards making GFP the vital tool it is today. Martin Chalfie, a biochemist, was researching the nervous system of the tiny, transparent roundworm *Caenorhabditis elegans* in the 1980s. This was an ideal model organism for studying various biological mechanisms, since its organs were visible in an ordinary microscope. Chalfie heard of Shimomura's protein at a seminar at Columbia University, and realised immediately that GFP could become a superb tool and act as a fluorescent tag for various events in the worm's different cells.

After the seminar, Chalfie phoned a number of scientists to learn more about GFP. The idea he then had, and succeeded in implementing, was to use genetic engineering to insert the gene governing GFP production into the worm's DNA, in a position immediately before the genes of the proteins that are active in the development of nerve cells. When the nerve cells began to be formed, GFP was also produced — and Chalfie was able to follow, under the microscope, how the green fluorescent nerve cells emerged.

Since then, GFP has revolutionised the work of scientists who seek an understanding of how life develops, as well as of various diseases. The fluorescent protein is used in a variety of species, from genetically modified mice to fish and banana flies. The colour palette available for researchers to work with has, moreover, been supplemented with proteins that glow in colours other than green. One of the scientists responsible for this advance was Roger Tsien, a biochemist, who shared the 2008 Nobel Prize in Chemistry for GFP with Shimomura and Chalfie. Using several markers of different colours makes it possible, for example, to study how different nerve cells are interwoven to form the complex network of the brain.

GFP is also used in environmental protection. Genetically modified bacteria can mark the presence of toxic arsenic in drinking water by starting to emit green light. One somewhat offbeat result of research on using fish to locate contaminants in aquatic environments is that fluorescent aquarium fish coloured with GFP are now on sale. Presumably, people are as fascinated by the luminous fish as Shimomura was by the jellyfish he began studying half a century ago. //

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THE ROYAL SWEDISH ACADEMY OF SCIENCES

THE ROYAL SWEDISH ACADEMY OF SCIENCES, 2012 // REPRINT MARCH 2017

Editor & author: Andreas Nilsson/Vetenskapsjournalisterna

Translator: Clare James/Språkverksta'n

Graphic design & illustrations: Ingrid Hernvall Creative

Cover picture: Petri dish with mould fungus of the *Penicillium* genus (iStock)

Photographs: Kajsa Kax Wåghals, photographer (pp. 8, 10, 20, 24 and 27), photographer Markus Marcetic (13), Fort Photo, iStock, Matton, Scanpix, Getty Images, Jannik Meyer, Frank Vinken, Albert Mihranyan, Maximilien Brice/CERN and Kevin Raskoff. The cover of *Science*, volume 263, issue 5148, is reprinted with permission from the American Association for the Advancement of Science (AAAS).

Printing & repro: Åtta.45. Paper: cover 200 g Scandia 2000 smooth white, body 130 g smooth white.

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THE ROYAL SWEDISH ACADEMY OF SCIENCES