Four Swedish issues of Medicinsk Vetenskap 2007.
The best articles are chosen for this English language edition of Medical Science.
Karolinska Institutet – A Medical University

Karolinska Institutet is one of the leading medical universities. It is also Sweden's largest centre for medical education and research, with 6,000 full-time students enrolled and 40 per cent of the academic medical research carried out in Sweden.

Research at Karolinska Institutet is of the highest international standard within a range of important fields. The research covers all of medicine, from public health and caring sciences to research into human genomics using advanced technological methods. In recent years particular success has been achieved in fundamental cell biology, including research into neural stem cells and the early development of the nervous system, research into several forms of cancer, into inflammation and infectious diseases, genomics, medical epidemiology, and global health.

Karolinska Institutet sets a high priority on quality and flexibility, in undergraduate and postgraduate education and in research. Other areas given a high priority are ethics, equality, and relationships with the world around.
“Our research success is founded on a long tradition of breakthrough discoveries”

Every year since 1901, an assembly of professors at Karolinska Institutet in Stockholm has selected the winner – or winners – of the Nobel Prize in Physiology or Medicine. Somewhere in the world top-flight researchers can rejoice at receiving the world’s most prestigious prize in science. They enjoy a period of celebration and glamour, with the eyes of the world focussed on the new celebrities.

However, for us who work in the field of biomedical research, the Nobel Prize means so much more than just honours and a fantastic party in the Stockholm City Hall. It makes researchers on all levels proud, and provides a spur to continue the search for knowledge and previously unknown truths. The journal Medical Science, which you are holding, describes, among other advances, how the technique of modifying or deactivating individual genes in laboratory animals, which was awarded the Nobel Prize in 2007, is used in everyday work at Karolinska Institutet. Few scientific advances have changed medical research so fundamentally as the development of knockout mice by Mario R. Capecchi, Martin J. Evans and Oliver Smithie. This issue contains an illuminating and interesting description of the significance of the knockout technique, and it describes selected highlights of the research that is currently under way at Karolinska Institutet. The world is becoming ever smaller, and this poses new limitless challenges for medical science. A study carried out by Karolinska Institutet and the Swedish Institute for Infectious Disease Control (SMI) has shown that travelling prohibitions can be very effective in preventing pandemics. Other research results that are highlighted in the journal suggest that a thorough analysis of requirements is vital when supplying aid to areas affected by major natural disasters.

Our scientists are willing to challenge what can be referred to as the “inner limits” of knowledge. A very interesting field of research that is still in its infancy is that of epigenetics, which throws doubt on all that we thought we knew about the relationship between nature and nurture. I hope that you will find this as interesting to read about as I did!

Harriet Wallberg-Henriksson
President of Karolinska Institutet
Research in pictures wins prize

The Lennart Nilsson Award 2007 went to American photographer and researcher Felice Frankel.

She was awarded the prize for creating images which are at once exquisite works of art and crystal-clear scientific illustrations – fascinating and valuable to the general public and scientific community alike.

“I love science,” said Frankel when talking about her pictures at Karolinska Institutet. “I want the world to love science. But I’m not an artist, I’m just a mouthpiece for science. My pictures do not work without a context.”

Frankel has devoted her work to uncovering previously hidden aspects of our surroundings in a scientific context. Examples of areas in which she has shown an interest are nanotechnology, magnetism and simple physical phenomena such as the surface tension of water droplets.

From the jury’s motivation: “Those viewing Ms Frankel’s images are initially captivated by their form and colour. No sooner is their curiosity aroused than they want to know what the photograph depicts. She has thus fulfilled a scientific reporter’s paramount task: to awaken people’s interest and desire to learn.”

World record for lung tests

No fewer than 2,882 people seized the chance to test their lung function for free during a two-day period in September 2007 at the busiest underground railway station in Stockholm. This broke the previous record set in Munich in 2006 when 2,042 people tested their lungs.

75-year-old Nils Malmlöf was one of those who took part. “I’ve smoked for 60 years and I thought I’d test my lungs now that I had the chance,” he said. “I’ve given up smoking for three whole winters, but now I’ve been advised to stop altogether, and I shall do just that. The test showed the beginnings of impaired lung function, and it would’ve been strange if there hadn’t been any signs of me having smoked for so long.”

The event was held in connection with the world’s largest meeting of lung specialists, the annual congress of the European Respiratory Society. It was project-managed by Anne Renström from the Centre for Allergy Research at Karolinska Institutet and Inger Kull from the Forum for Public Health at Stockholm County Council, with financial support from the European Lung Foundation.

Nils Malmlöf plans to quit smoking after 60 years.
A new research collaboration between Karolinska Institutet and AstraZeneca has already borne fruit. For the first time there is the possibility of studying one of the brain's most important signalling systems, the glutamate system, in living people.

Glutamate is one of the most common signalling substances in the human brain and is involved in virtually all brain functions. However, although scientists’ PET scanners can image other important signalling systems, such as the dopamine and serotonin systems, it has not previously been possible to capture images of the glutamate system due to the absence of a suitable tracer which can bind specifically to the receptors in the glutamate system.

Now AstraZeneca and Karolinska Institutet together have developed a tracer which makes it possible for the first time to study the glutamate system in the brains of living people.

“All of the antipsychotic medicines on the market act on the dopamine system, but it may very well turn out that glutamate receptors are even better targets for medicines. As part of the collaboration, an ultramodern PET scanner has been purchased for use in both academic and pharmaceutical research,” says professor Lars Farde at AstraZeneca.

“The new PET scanner allows us to study the brain in much greater detail than before,” says professor Christer Halldin from Karolinska Institutet.

Find out more about how the PET scanner will be used on pages 23–25.

Panic stems from reptilian brain

New research shows that humans faced with different degrees of threat handle the situation with very different parts of the brain.

Animal experiments have shown that animals faced by a particular threat shift between different brain conditions and behavioural patterns depending on whether the threat is distant or immediate. By mimicking the sense of being hunted in the laboratory, Swedish and British researchers have shown for the first time that humans work in the same way.

The hunt situation was recreated by having volunteers play a Pac-Man-like TV game where a character is steered through a labyrinth and hunted by another. To get the volunteers, whose brain activity was monitored the whole time, to feel a real sense of being hunted, the game was spiced up with electrical shocks. These shocks were not harmful, but sufficiently unpleasant to induce a kind of brain process which the researchers recognise from experimental animals experiencing acute danger.

When the pursuer appeared some way away in the labyrinth, activity increased in the volunteers’ frontal lobe, the part of the brain which handles planning and advanced decision-making. But when an attack came closer, the more basal brain stem was activated instead, and the higher processes were blocked.

“The evolutionary explanation is that it’s good to prepare if there’s time, but when fear is acute, the brain stem ensures rapid action,” explains Predrag Petrovic, one of the researchers behind the study. “The same thing happens when an antelope spots a lion on the savannah. The antelope reacts with increased passivity right up until the lion comes sufficiently close to attack. Only then does the antelope bolt.”

Petrovic, who normally conducts his research at Karolinska Institutet, developed the experimental model together with colleague Dean Mobbs at the Wellcome Trust Centre for Neuroimaging in London.
Two rods and a pair of video cameras linked to two displays are all that is needed to give someone a realistic out-of-body experience. Researchers at Karolinska Institutet are fooling the human brain and learning more about the relationship between body and “self”.

Text Ola Danielsson

How to fool your self

“The idea came to me when I was bored during a lecture as a medical student. I began to wonder what would happen if you could move a person’s eyes to a different place in the room. Would the sense of self follow the eyes or stay in the body?”

Henrik Ehrsson could have left it as a daydream, but he did not. Six years later he is still trying to understand what role our senses play in our sense of self, but now in the capacity of research leader at the Department of Clinical Neuroscience at Karolinska Institutet. Through a simple but ingenious experiment involving just such an “eye transfer”, he recently managed to give volunteers a strong sense of being outside their own body.

“The idea was that the visual aspect is important in how the brain knows where the self is,” he explains. “As the eyes are always attached to your skull, they send very reliable information to the brain. By looking at my surroundings, I get not only information about these surroundings but also about where I am within them.”

The experiment requires a volunteer to sit on a chair and look into two displays mounted in front of his eyes. These displays are linked to video cameras located a couple of metres behind the volunteer and pointed at him. When the cameras are turned on, the volunteer sees the world from the cameras’ “robot eyes” and gets to see himself from behind.

“It’s a very strange experience seeing yourself from the outside, but it doesn’t give any real illusion of your self moving outside your body,” says Ehrsson. “It’s a bit like seeing yourself on a CCTV screen in a shop, although the experience is enhanced by the stereoscopic vision offered by the two cameras.”

So the question from his student days was finally answered: if you move a person’s eyes, the sense of self stays with the body. But it also turned out that a proper out-of-body experience was not a very big step away. It is a matter of getting the volunteer not only to see but also to feel his self outside the physical body. The researcher can do this simply by standing in front of the cameras and pointing with a rod at a point immediately beneath them – that is to say at the chest of the “phantom body” (the illusory body located just behind the volunteer’s physical body) – while poking the volunteer’s actual chest without him seeing this.

“The brain then reacts to the hand touching the illusory body, giving the volunteer a strong sense of being located a couple of metres outside his own body. In other words, the self has moved two metres across the room and left its real body, which feels instead like an empty shell or doll.”
We humans normally have no problems knowing where our “self” is. The rule of thumb is that we are always in exactly the same place as our body.

“I’m studying the self at the most basic level, which is the sense of being a body,” Henrik Ehrsson says. “But the self also has a number of higher levels to do with our memories, our social characteristics and our skills. All of this together makes up what we would call our self in everyday talk.”

In day-to-day life our perception of our own body is self-evident, but scientifically it is far from unproblematic. Bodily self-awareness requires what is known as multisensory integration, which means that signals from our eyes, muscles, skin and sense of balance are moulded together in such a way that the brain can create a representation of the body and its position in our surroundings – an ability which is shared by all animals capable of differentiating between themselves and their surroundings. The brain’s perceptual system seeks constantly to create a model of our surroundings and a model of our body. This model is
If we can get the surgeon to feel that his self has moved into the other operating theatre, he'll be able to do a better job as a surgeon."

based on interpretations of sensory impressions, and sometimes the brain misinterprets them.

"By manipulating the inflow of sensory signals, it's very easy to fool the brain so that you experience dramatic changes in your bodily perception," says Ehrsson.

His latest experiment shows that vision and touch are sufficient sources of information for the brain to decide where our self is located spatially. When the visual impression is combined with the corresponding touch impression, the illusion of spatial transfer is complete. The self is now where the cameras are, not where the body is. Henrik Ehrsson says that this discovery could have a number of practical applications.

"It could be very useful to transfer our perception of self to external objects. One example might be transferring the perception of self to an artificial arm, so that the patient perceives the prosthesis as his real arm. It could also be used for remote surgery, where a surgeon controls two robot arms in a different operating theatre, maybe many miles away. If we can get the surgeon to feel that his self has moved into the other operating theatre, he'll be able to do a better job as a surgeon."

But the main aim is not to manipulate the brain but to understand how it works, both when it is healthy and when it is sick. Out-of-body experiences are not normally induced in a laboratory environment, but are sometimes reported by patients with diseases such as epilepsy.

"There are various theories about how these out-of-body experiences occur," explains Ehrsson. "Some put them down to a kind of dream experience or overactive imagination. But there is also much to suggest that out-of-body experiences are a natural result of the integration of sensory information being disrupted for some reason. For example, if the sense of balance is manipulated to make you feel that you're spinning around, the brain can be forced to construct a corresponding visual experience, maybe from something that isn't actually there."

It is known that injuries in the multi-sensory regions of the brain can result in disturbances in our body image. There are various types of brain damage which can cause parts of the body to feel twisted or no longer part of the person's own body.

"I'm actually less interested in out-of-body experiences than in the natural in-body experience that we have in our everyday lives," says Ehrsson. "The illusion is just a way of changing it so that we can try to understand it."
Professor of international health lists

Five common myths about the world

1) “Malnutrition and infection are the biggest health problems”

“Hunger and infection are still incredibly common among the two to three billion poorest in the world, but as standards of living gradually improve, chronic non-communicable diseases, mental disorders and accidents are becoming the biggest global health problem. Did you know, for example, that the commonest cause of death among young women in many parts of India and China is suicide? The new drug supply challenge is that people in middle-income countries will be able to afford diagnoses but not the best treatment for diseases like diabetes and depression.”

2) “People in developing countries have large families”

“In 1972 the average woman in Bangladesh gave birth to seven children! But today the average for the same country is less than three. Families with two or three kids are now most common across the world. Women have roughly the same number of children in Vietnam as in Sweden – around two. The number of children born per woman is still high in many African countries, but not in all of them! In Botswana and South Africa, for example, the average is around three children per woman.”

3) “Climate change is the biggest environmental problem today”

“No, climate change is the biggest environmental problem we will suffer from tomorrow! In terms of health, indoor air pollution due to fires with no chimneys is still a bigger problem. But water contamination is probably still the biggest global environmental problem. Around two billion people regularly drink their neighbour’s lukewarm faeces – and solving this problem is as urgent an environmental challenge as climate change!”

4) “The well-educated are mainly in the West”

“Tomorrow’s academics are currently being educated in India and China. People think that Asian manpower is for shoe factories and call centres, but the software for these call centres is actually developed in India. In the next decade, India and China will produce more chemistry and physics graduates than Western Europe and North America. They get lower salaries, but have the same skills and mostly work harder.”

5) “People die young in developing countries”

“Average life expectancy has risen in the world. For example, it is now 75 years in Mexico and 71 in China. Although Vietnam is still a relatively poor country, life expectancy there is approaching 70 years, the same as in the USA a generation ago. In African countries, though, life expectancy is still low, partly due to HIV and high child mortality. The situation is worst in war-torn Sierra Leone, where life expectancy is estimated to be around 40 years and around a third of all children die before reaching the age of five.”

Crusade for better information

Hans Rosling is the professor who co-founded Gapminder, which sold its statistical software to Google. At present, he is on sabbatical from his professorship at Karolinska Institutet and working with Google.org in San Francisco on a project to improve access to statistics on the world’s two billion poorest.

Rosling began his crusade for better information about world health around a decade ago when he discovered that medical students at Karolinska Institutet knew less about the world than chimpanzees.

“A chimp has a 50 per cent chance of choosing correctly between two alternatives,” he explains. “But my students got fewer than half right when I quizzed them on child health in different countries!”

Rosling’s conclusion is that many people are not just ignorant about how the world really is today, they also suffer from outdated preconceptions about the world. We are quite simply not keeping up with global developments. Did you know, for example, that child mortality, the number of refugees and the proportion of people living in poverty around the world are all in decline?

The injustices of this world are still lamentably vast, but he does not agree that things are getting worse.

“There is still a frightful amount of unnecessary suffering, but things are actually getting better for most people,” he says.

“A billion people live as we Swedes do today; three billion as we did a century ago; two billion as we did two centuries ago; and half a billion as we did three centuries ago when a warlord was king of Sweden. Changing the world for the better takes time, but I think mankind is in the process of doing it!”

Cecilia Odlind

Find out more about how the world really is today at www.gapminder.org.
When a person develops cancer, the body’s immune defence is activated to destroy the tumour cells. By removing the most effective defence cells from the body, multiplying them and then returning them to the patient, scientists can help the body to fight the cancer itself. This immunotherapy is now being tested on several different types of cancer.

**Body’s own cells**  
a new way to fight cancer

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**Immunotherapy is about** giving the body’s own defences a head-start. When a tumour develops, the immune system normally starts to try to fight the cancer. But it does not always succeed, as tumour cells have various ways of getting round the body’s defences. For several years scientists at Karolinska Institutet have been working on a way of helping the body’s defence cells – lymphocytes – to beat the tumour.

Tumours spread through the body when tumour cells become detached and travel through the lymph vessels to the lymph nodes. The new method is based on identifying the “sentinel node” – the first lymph node draining the tumour. Virtually all of the body’s various types of lymphocytes will be found here. These kill invaders such as viruses and bacteria, and can also destroy tumour cells. In this way they protect the rest of the body against the spread of the tumour by fighting tumour cells arriving through the lymphatic fluid. The cells on which the scientists at Karolinska Institutet have been focusing are known as CD4 cells.

“CD4 cells stay in the body and remember a tumour for the rest of our lives, even after treatment is finished and the tumour has disappeared,” explains researcher and surgeon Magnus Thörn. “They act as a vaccine against that particular type of tumour.”

To get hold of the cells which are active against a tumour, the sentinel node where they will be found needs to be identified. This is done by injecting a blue dye around the tumour, which then spreads through the lymph. The first lymph node is soon revealed because it turns blue. The scientists can then remove the CD4 cells from the sentinel node and identify the ones which are active against the tumour. These cells are cultured in the laboratory together with parts of the tumour and other substances from the body to stimulate them to divide and multiply. Some 400-500 million cells can be grown over the next 28 days and then returned to the patient through a blood transfusion. This method – known as the SentoClone method – has managed to increase the survival of patients with metastatic colon cancer by more than 18 months relative to the standard treatment.

“We’ve been able to reduce or even eliminate tumours in these patients, both solid tumours and metastases where the cancer has spread,” says Thörn. “As the cells come from the patients themselves, we haven’t seen any side-effects, which can be very severe with other forms of cancer treatment.”

Together with Ola Winqvist, associate professor of clinical immunology at Karolinska Institutet, Thörn has also started up a company, SentoClone AB, to develop the method. The results to date come from a small unpublished study. The next step is a...
larger study of 80 patients with colon cancer at ten different hospitals, as well as smaller studies of malignant melanoma, bladder cancer and ovarian cancer.

If the sentinel node is free from tumour cells, this is a sign that the cancer has not yet spread. However, if it does contain cells from the tumour, this means that metastases may have taken place and that the cancer is also to be found in other parts of the body, Magnus Thörn explains. This led him to ponder the reasons why a tumour does or does not spread.

“Our hypothesis is that it’s not the tumour’s aggressiveness which determines whether it spreads in the body, but the properties of the lymphocytes which fight the tumour,” he says. “We know that the lymphocytes in patients with metastatic cancer have reduced activity. It has also been shown that patients with lots of CD4 cells in the tumour live longer.”

Recently the researchers reported that they had been able to find similar defence cells in the lymph nodes of patients with ulcerative colitis. These patients sometimes develop the early stages of cancer and run an increased risk of bowel tumours. The researchers hope that immunotherapy may also be useful in reducing the risk of future cancer in these patients.

CANCER THERAPIES USED TODAY:

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<tr>
<th>Therapies</th>
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<tr>
<td>Surgery</td>
<td>Cures if the cancer has not spread</td>
<td>Only really works before the cancer spreads</td>
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<td>Radiotherapy</td>
<td>Rapid treatment, surgery not required</td>
<td>Severe side-effects at high doses, not all tumours respond</td>
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<tr>
<td>Chemotherapy</td>
<td>Effective against some types of tumour, well studied</td>
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<td>Immunotherapy</td>
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Every minute a woman somewhere in the world dies from complications of pregnancy or childbirth. Only 1 per cent of them are in high-income countries. Most bleed to death at home far from a hospital, and there is a major shortage of health workers. A new category of nursing staff with some additional surgical training can save lives, says Staffan Bergström, professor of international health at Karolinska Institutet.

**Effective non-physician clinicians save lives**

The UN has set a target of reducing maternal mortality worldwide by 75 per cent by 2015.

“Forget it!” says Bergström. “In Africa as a whole, maternal mortality is not falling at all at the moment. In some African countries, it is actually increasing, in some cases even doubling.”

But there are also examples of the opposite. In Mozambique, maternal mortality has more than halved in the past 15 years. One of the reasons may be the availability of nursing staff with some additional surgical training known as técnicos de cirurgia. This cadre of non-physician clinicians came about out of sheer necessity during the civil war which ravaged the country following its independence in 1975. Caesarean sections have to be performed even in a country in crisis, and often only nurses and midwives were available. Staffan Bergström was there and spotted the potential in quickly training up skilled health workers, and in 1984 a three-year supplementary training programme started up for nurses wishing to learn surgery. A total of 62 técnicos de cirurgia have now been trained in Mozambique. These can even carry out major surgical procedures following road accidents, delivery complications or burns. The aim is for there to be at least one such practitioner at every small hospital. Similar partially trained surgeons can also be found in other African countries, including Malawi, Zambia and Tanzania.

According to a report from the WHO, there is currently a shortage of around a million health workers in Africa. The few doctors who qualify often head to the cities in search of more bearable living conditions, and many are tempted abroad where they can expect much better pay and career development opportunities. The results of a new study in Mozambique carried out by Staffan Bergström’s research team show that all doctors had left hospitals in rural areas within seven years of completing their training, while 88 per cent of the técnicos de cirurgia remained.

“Maternal mortality is highest in rural areas, which is where the health workers need to be,” he says. “It’s expensive to train people who do not then stay where they’re needed the most.”

However, investing in training up técnicos de cirurgia is proving cost-effective. This has been shown by Bergström and his colleagues, including postgraduate student Caetano Pereira, in another recent study where they compared the cost of medical doctors with the cost of técnicos de cirurgia. The results show that técnicos de cirurgia cost less than a third of what doctors cost per major surgical obstetric procedure: 39 US dollars as opposed to 144.

“Higher salaries and seven years of...”

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**Women’s lifetime risk of dying due to pregnancy or childbirth:**

- **Lowest:** Sweden – 1 in 30,000
- **Highest:** Sierra Leone – 1 in 6
- **In Africa:** 1 in 16

The vast majority are “low-risk mothers” whose disease (complication of pregnancy or childbirth) could not have been predicted. **Source:** WHO
Emilia Cumbane, a midwife in Mozambique, prepares to perform a caesarean section.
training rather than three mean that doctors cost much more,” says Bergström. “The fact that doctors are more likely to move to the cities or be recruited abroad also makes them an expensive affair for these countries.”

He hopes that the results of the study will inspire politicians to show faith in técnicos de cirurgia as a cadre. But training non-physicians to do what was previously the exclusive domain of physicians has not come without protest. There have been objections, partly from the African countries themselves, believing that this results in poorer care for Africans. Bergström disagrees:

“The individuals we’ve trained are hand-picked and already have enormous experience,” he says. “In one study, we compared the outcome of a thousand caesarean sections performed by doctors with a thousand performed by técnicos de cirurgia. The results showed no difference in infant or maternal survival or in subsequent hospitalisation. Despite problems with infection and malnutrition, serious complications were very rare in both groups.”

The técnicos de cirurgia have themselves protested against their low salaries and their lower status relative to doctors. In their study, therefore, the researchers worked out what it would mean in terms of increased costs if the salaries of técnicos de cirurgia were to be doubled. Even then, the cost per major surgical obstetric procedure is less than half that for doctors: 60 US dollars as opposed to 144. Bergström says that working conditions in rural areas also need to be improved:

“As one of my students put it when talking about the housing offered at district hospitals to him and his colleagues: ‘Even cats would run away from these houses!‘ To get people to stay out here in rural areas, there needs to be the possibility of a bearable existence and functioning communications.”

However, maternal mortality in Mozambique is still about a hundred times higher than in Sweden, which is one of the world’s very safest countries in which to give birth. More health workers per capita and a better distribution of them across the country are one way of reducing maternal mortality, but other measures, often relatively simple and cheap ones, are also needed.

“Pregnant women and those around them need to be taught always to seek medical attention if the woman experiences bleeding, fever or pain or if her waters break,” says Bergström. “To reduce maternal mortality, the AIDS pandemic also needs to be stopped. But a lot of it is about simple measures to improve hygiene, access to blood, antibiotics, and trained medical personnel.”

Publications:

The cost effectiveness of surgically trained assistant medical officers in performing major obstetric surgery in Mozambique
Kruk M, Pereira C, Vaz F, Bergstrom S

Meeting the need for emergency obstetrical care in Mozambique: Work performance and work histories of medical doctors and assistant medical officers trained for surgery

Maternal mortality ratio in Sweden:
- 1750: 1,000
- 1900: 300
- Today: 4–6
The maternal mortality ratio is the number of maternal deaths per 100,000 live births.

How can we reduce maternal mortality?
1. Provide good nutrition for pregnant women and new mothers
2. Provide access to quality care during childbirth
3. Provide contraceptives
Source: Save the Children

Non-physician clinicians
Non-physician clinicians (NPCs) is an umbrella term for non-doctors who perform often advanced surgical and other clinical procedures which normally require a doctor. In a recent study published in The Lancet, it was found that this cadre is well-established in 25 out of 47 countries in Africa (53 per cent).

Even in a country like the USA, there are around 100,000 physician assistants, a kind of NPC. Uganda, Kenya and Malawi are the countries with the greatest density of NPCs, but several other countries have far-reaching plans to counter the shortage of doctors with large-scale training of NPCs.

Source: Staffan Bergström
New research shows that the cells in our bodies remember what they have experienced, and suggests that environmental effects can be passed down the generations – without any of it being written into our genes. Modern epigenetics has turned textbook heredity theory on its head.

*Text Ola Danielsson*

It is a well-established fact that individual human beings have no possibility of influencing the biological inheritance they pass on to their children. The reason for this is that the genetic material found in the sex cells – the genetic code – is well-protected from most forms of environmental influence.

So there was considerable surprise in 2006 when a study suddenly seemed to contradict this. After studying the population register, researchers were able to demonstrate a clear link between the diet of inhabitants of a small village in Överkalix in the far north of Sweden around the turn of the 20th century and their grandchild-
ren’s risk of cardiovascular disease a century later. Men whose grandfathers were poor run a lower risk of being affected, while those whose grandfathers ate better run a higher risk. Classical genetics cannot explain how a typical environmental factor – diet – has been able to leave an imprint which has been passed down two generations. Something has undeniably been passed on – the question is what.

The answer to this and similar questions is now being sought through epigenetics, a new research field which is busy transforming our view of heredity. In epigenetics, it is no longer a truth that heredity is synonymous with genes. We do indeed inherit our genes, but now researchers believe that we also inherit something else – namely instructions for how, when and where the genes we have are to be used. This information is hereditary but is not always stored in the DNA sequence, or genome, but in what is known as the epigenome. “Epi” is Greek for “additional”, and epigenetics can be seen as a supplement to genetics. In molecular terms, the epigenome can be said to consist of different patterns in the chemical packaging which protects and to some extent hides the long DNA molecules in the cell nucleus. When the epigenetic pattern changes, different parts of the DNA sequence become exposed and available for decoding.

According to Tomas Ekström, professor of molecular cell biology specialising in neuro-oncology at Karolinska Institutet, epigenetics is behind basic functions in all living organisms. It explains, for example, how there can be different types of cells in the body.

“The epigenome is the cell’s operating system,” he explains. “There are two metres of DNA in every cell, but there are no types of cell where all of the genes are active at the same time. Right from the very beginning, in the fertilised egg cell, the genome is open to negotiation – it can become anything. What happens during our development is that the different cell types are locked into different epigenetic programs.”

Early on in our development, a kind of memory emerges in various types of cells which is physically located outside the genetic code and governs genetic expression. As these epigenetic memories are copied and passed on together with ordinary DNA – but do not themselves consist of DNA – they constitute a special form of heredity, albeit at the cellular level. But does it actually make any difference if information in my body is passed on by some molecule or other? Yes, actually it does. One important difference is that epigenetic conditions are dynamic and can change rapidly in response to external environmental influence. This means that even if the DNA sequence remains the same, our genes can, in practice, change the way they work depending on what we experience during our lives – in other words, exactly

**One DNA – multiple cell types**

All of the cells in the body carry the same DNA sequence – the same genes – and should therefore, according to classical genetics, be identical. But they are not – the body consists of many different types of cells which all differ from one another. This is because each cell carries an epigenetic code which is common only to cells of the same type. A person’s DNA sequence is established back in the fertilised egg cell (1) and is then passed on to all of the cells in the body. During the first few days of the embryo’s development, no epigenetic changes have yet taken place, and so all cells are absolutely identical (2). For reasons which scientists do not yet fully understand, epigenetic modifications of genetic expression then occur, giving cells different characteristics (3). Once an epigenetic modification has taken place in a cell, this will be copied during cell division and be passed on stably to all daughter cells.
what conventional genetics rules out. Epigenetics can therefore partially bridge the old gap between inheritance and environment. Tomas Ekström believes that epigenetics will yield new insights into diseases where genes and environment interact.

“Epigenetics is truly the link between inheritance and environment,” he says. “Besides the direct impact of environment on DNA, for example in the form of mutations, all environmental effects which influence genetic expression act through epigenetic mechanisms. How, for example, can only one of two identical twins develop diabetes or schizophrenia? They have the same genome, so it must be down to some kind of environmental influence. If we understand these mechanisms, we can learn to affect the outcome, and epigenetics gives us a molecular handle for doing so.”

In his research, Ekström is attempting to understand how epigenetic changes can lead to cancer.

“I jump every time someone says that cancer is a genetic disease,” he jokes. “The first thing to happen when non-hereditary cancer arises is probably epigenetic changes which subsequently destabilise the interpretation of the genome. The genetic changes we associate with cancer occur only later.”

There is much to suggest that epigenetic changes caused by environment can affect future generations, which could explain the remarkable results from the Överkalix study.

“The prevailing view is that the epigenome is deleted when the sex cells form,” says Ekström. “The genome is reset to zero, rather like pressing the reset button on a computer. But there seem to be things which escape deletion.”

Research shows that this is at least the case in rats. In an American study, scientists exposed a pregnant rat to a dose of a pesticide known to cause reduced sperm quality, which was duly observed in the male offspring born shortly thereafter. More remarkable was that their offspring in turn had reduced sperm quality, and that this deterioration even persisted for another generation. The conclusion was that the treatment resulted in a different pattern of DNA methylation which affected gene expression, and that this change was passed on.

Tomas Ekström believes that it is only a matter of time before we begin to understand that epigenetic mechanisms are linked not only to disease but also to our behaviour.

He mentions animal experiments carried out by Canadian researcher Moshe Szyf and colleagues which show that behaviour can be “quasi-inherited” through epigenetic mechanisms. In an experiment, baby rats treated “lovingly” by their mothers underwent an epigenetic change in gene expression which made them receptive to a particular hormone and so less susceptible to stress. If the baby rats were brought up instead by a different kind of mother who gave them less attention, this epigenetic change did not take place and there was no cellular inheritance.

It is a long way from experiments on rats to human beings, but epigenetics shows that inheritance and environment are more closely linked than has long been believed. Nor is it inconceivable that epigenetics will show that we are linked to previous generations in ways which we cannot yet imagine. They say that you are what you eat, but it may be that you are also what your parents and grandparents ate.
Using stem cells to repair the heart after a heart attack is a method which could one day be a reality, hope scientists from Karolinska Institutet. By replacing the damaged tissue with stem cells, the risk of the patient suffering from heart failure is reduced.

Text **Ann-Marie Dock**

Repairing the heart

**Following a heart attack**, the muscle cells are replaced with scar tissue. The result is that the heart becomes enlarged, its pumping capacity is impaired, and the patient can suffer from heart failure. Currently patients are treated with balloon angioplasty or a bypass operation in combination with drugs. In the future, treatment with stem cells might be an alternative.

Karl-Henrik Grinnemo, a researcher at Karolinska Institutet and specialist in thoracic surgery at Karolinska University Hospital, is one of those who have looked more closely at the treatment possibilities which stem cells could offer. He has studied three different types of stem cells and their ability to develop into cardiac muscle cells (cardiomyocytes) and affect cardiac function following a heart attack. He has also looked more closely at various rejection reactions. The results were presented in a recent doctoral thesis at Karolinska Institutet.

**One of these** three cell types is human mesenchymal stem cells. These are found in the bone marrow and can develop into muscles and blood vessels, among other things. Another is human embryonic stem cells. The third is a kind of precursor to cardiomyocytes and goes by the rather unwieldy name of human foetal cardiomyocyte progenitor cells (HFCPs). These are found in the heart of the foetus, but disappear after birth and must therefore be cultured from aborted foetuses. Grinnemo and his research team, under the supervision of professor Christer Sylvén, are the first in the world to identify these cells,
In the future, stem cells may be able to replace damaged tissue following a heart attack. Scientists at Karolinska Institutet were the first in the world to identify the cells in this image, which are the earliest precursors to cardiac muscle cells (cardiomyocytes). The hope is that these cells can be transplanted to damaged hearts to reduce the risk of the patient going on to suffer from heart failure.

with stem cells

which are the earliest precursors to cardiomyocytes.

Their studies have found that these immature foetal cells (HFCPs) are the type of cell which appears to be the very best at repairing damaged hearts. Grinnemo has managed to culture these cells and get them to form spherical clusters (cardiospheres) and carpets of spontaneously beating cardiomyocytes. These proved capable of forming stable transplants in the hearts of laboratory mice, and generated mature ECG signals. One drawback is the limited availability of this type of cell.

“But we hope to be able to start up clinical studies within a few years,” says Grinnemo.

The other two cell types, mesenchymal and embryonic stem cells, both caused various types of problem. They did not develop into the desired cell type, namely cardiomyocytes, and they often led to rejection reactions. This is a big disadvantage for patients, as strong medication is then needed to suppress the immune system.

“The rejection of the embryonic stem cells was probably because they developed in the heart into other types of cell which expressed proteins to which the mice reacted,” explains Grinnemo.

However, he believes that the rejection problem can be resolved. There are already methods available for fooling the immune system so that it is possible to create a certain amount of tolerance without needing to use immunosuppressant drugs. These methods are currently being tested in the USA in clinical studies of kidney transplantation, with good results to date. Karl-Henrik Grinnemo hopes to be able to start up a clinical study of mesenchymal stem cells as well within a year or two using the patient’s own stem cells in order to avoid rejection.
A ban on journeys of more than 50 kilometres could reduce the spread of serious diseases such as SARS by up to 50 per cent. This is the conclusion drawn by scientists at Karolinska Institutet and the Swedish Institute for Infection Disease Control after studying the results of thousands of computer-simulated SARS outbreaks. According to the simulations, travel bans have an effect even if a third of the population ignore them.

**Text Ola Danielsson**

**Travel restrictions effective against spread of infection**

In early 2003 there were real fears that the lung disease SARS (severe acute respiratory syndrome) would spread out of control worldwide. The first cases were reported in Hong Kong and Vietnam in February 2003, and when reports soon followed from Taiwan and Canada, the world began to view the new disease as a major threat. Five months later, though, the WHO could confirm that the outbreak had been brought under control. By then, SARS had been spread by travellers to more than 30 countries on all continents and infected 8,400 people. Most of those affected were in China and Hong Kong where the outbreak was most out of control. Part of the reason why SARS did not become established in other countries was the WHO’s far-reaching travel warnings, which resulted in a sharp decrease in air traffic to and from the places affected. However, it is unknown exactly what effect these recommendations had. It is also doubtful whether these strategies can be applied in future situations or in other places. How, for example, should an outbreak starting in Stockholm rather than Hong Kong be handled?

To answer this question, Martin Camitz and Fredrick Liljeros, researchers at Karolinska Institutet and Stockholm University, used computer simulations to try to recreate the SARS outbreak within Sweden’s borders. The model used data for all travel between municipalities made by around 17,000 Swedes during a two-month period. All straightforward journeys between municipalities were included, whatever the purpose, destination or mode of transport. Once the model had been developed, the scientists tested various scenarios where the disease broke out in Stockholm and travel restrictions between towns and cities were gradually introduced to curb its spread. After having the computer generate thousands of possible scenarios, they were able to draw the conclusion that travel restrictions are highly effective against SARS and similar diseases.

“When we allowed travel to carry on as normal in our simulations, the disease spread to most Swedish communities within 60 days,” explains Camitz. “But when we took out all journeys of more than 50 kilometres, the spread was much slower, and when we removed all journeys of more than 20 kilometres, the disease barely managed to get beyond the Stockholm area at all.”

That travel restrictions are a good means of combating the spread of infection is nothing new. According to Camitz, however, the restrictions and recommendations used today focus on reducing the total number of journeys without taking account of the length of these journeys. The simulations also showed that it is not necessary to eliminate all long-distance travel: it is enough to cut long journeys by around 70 per cent to have a positive effect.

“If this is translated into practice, –
How Swedes travel between the country’s 289 municipalities. The colours for each route indicate the intensity of travel, from dark red (minimum intensity = 10 journeys per day) to red, yellow and white (maximum intensity = more than 10,000 journeys per day). The images on the right show only journeys of less than 50 and 20 kilometres respectively.
»Human behaviour is the hardest thing of all to model. There’s nothing to say that people will behave the same way tomorrow as they did yesterday. People are quite simply unpredictable, and this is particularly the case in unusual situations such as the outbreak of disease.«

there’s no need for blanket travel bans,” says Camitz. “It might be enough just to issue recommendations, provided that most people follow them.”

However, as this is a model, the results cannot be applied directly to reality. But the link to reality is relatively strong, as the simulations are governed by realistic assumptions based on scientific observations. The information on how Swedes move around the country came from a major survey carried out in 1999, and the incubation period, contagiousness and spread pattern for the virtual disease was based on experience from the real SARS outbreak in 2003. But Camitz stresses that it is impossible to create a model which takes account of every single aspect of reality.

“Human behaviour is the hardest thing of all to model,” he says. “There’s nothing to say that people will behave the same way tomorrow as they did yesterday. People are quite simply unpredictable, and this is particularly the case in unusual situations such as the outbreak of disease.”

It turns out that one effective way of dealing with this problem is to allow people to behave in the simplest possible way – randomly. In the simulations performed by Martin Camitz and Fredrik Liljeros, people therefore move around within each community like particles in a gas. This means that each inhabitant in a given community has an equal chance of coming into contact with, and so infecting or being infected by, every other inhabitant of that community.

Camitz says that another option would have been to introduce some type of structure within these communities, such as families, schools and workplaces. It would then have been possible to pick out the people most likely to infect one another, such as pupils at the same school. With some diseases, such as chlamydia, the model would need to keep track of detailed networks of personal contact in order to work. For other diseases, it is more important that the big picture is correct – for example, that the model shows how people in general move between localities.

“At a low level, such as within a municipality, SARS and other moderately infectious airborne diseases spread in a way which our random model describes well,” says Camitz. “However, it was important to describe the travel pattern between the model’s 289 municipalities in detail.”

Although reality will always be more complex than these models, Martin Camitz believes that there is much to be learned from these simulations.

“Decision-makers need to take account of many other factors on top of those we’ve examined when they decide on a suitable strategy, but our results are definitely something to be factored into the equation.”

Without any travel restrictions, a SARS outbreak will have spread from Stockholm to most of Sweden’s municipalities after 60 days (left). But if journeys of more than 50 kilometres are banned, the spread is slowed (centre); and with no journeys of more than 20 kilometres, the outbreak does not get beyond the Stockholm area (right). The colours indicate the number of cases of the disease, and the red circle shows the average spread of the epidemic from Stockholm.
If we can build a system which behaves like the human brain, we will also have understood the brain itself. This is the basic tenet of computational neuroscience, a rapidly growing research field where supercomputers are used to recreate activity in the human brain.

In Sweden, this field has now been given a strong platform in the form of the Stockholm Brain Institute (SBI), where a supercomputer has recently been installed. Scientists at the institute are now ready to embark on the development of the most advanced models yet. According to Martin Ingvar, professor of cognitive neurophysiology, these simulations will provide a more in-depth understanding of the brain and its diseases.

“At present we know roughly which parts of the brain do what, but we can’t say how this happens,” he says. “The brain is the most complex structure we know, and to really understand the brain as a system, we need to use mathematical models.”

The scientists will use the computer to fuse together what they have learned about the brain in a dynamic system – a kind of holistic picture of the brain. The model will make it easier to grasp how different parts of the brain interact with one another. This, in turn, is essential for a better understanding and better treatment of diseases of the brain.
“The systems in the brain strive for equilibrium but sometimes go out of balance,” Ingvar explains. “We know, for example, that in depression some parts of the brain become very overactive, and this hyperactivity drops back as you recover, whether this is due to time, therapy or medicine. But we don’t understand why this hyperactivity occurs, or how it is related to the symptoms of depression. The idea of these models is to create a more mechanistic image of the brain so that we can understand why the brain ends up in a particular state, and how balance can be restored.”

Anders Lansner is a professor at the Royal Institute of Technology and one of the founders of the SBI. He has spent 20 years modelling the brain and says that the fundamental principle is straightforward. The first step is to model a single nerve cell in the computer, which basically means describing selected properties of the nerve cell mathematically.

“We know an awful lot about what individual nerve cells look like and how the transfer of impulses between nerve cells functions, and this can be described mathematically as a network of electrical circuits,” he explains. “A model of a nerve cell is quite simply an electrical network which corresponds to the nerve cell and its projections.”

Using the computer, the scientists will build up a 3D network of simulated nerve cells which mimics the real brain’s anatomy. By conducting various types of simulations, the scientists can study how different types of signals spread through the network. It will then, for example, be possible to get an idea of what happens when a drug is allowed to act on a particular receptor system. A well-designed model is an invaluable tool in understanding the brain’s complex signal traffic.

As the model is developed, it will also become clear where the most important gaps in our knowledge are to be found. When the model gives results which go against what we already know about the brain, it will need to be corrected with new data, and by comparing alternative models the researchers can find the most critical research topics. In this way, the number of experiments, which are often complex and time-consuming, can be kept to a minimum, and the accumulation of knowledge can be accelerated.

Anders Lansner believes that biological modelling will provide answers to funda-
mental questions about how the brain works.

“Much of our work is about questions to do with memory,” he says. “There are at least two different theories about our working memory which are now being investigated through simulations. One says that the working memory stores information by sustaining the activity in a certain group of cells, while the other says that memory storage also involves a rapid change in the structure of the brain in the form of strengthened synapses. If these models can help us to show which theory is correct, we will definitely have increased our understanding of the brain.”

The development process could continue right up until all of the results of brain research can be found integrated into a single model of the entire human brain. This is, in any case, the aim of the huge Blue Brain project started up by computer company IBM in conjunction with Swiss university EPFL. For a number of years now, they have been simulating nerve cells from the bottom-up, in other words from molecular level, and they do not plan to finish until they have built a virtual version of the whole of the natural brain.

As yet, a complete model is far from becoming a reality. At the current rate of development, it will be at least 20 years before it is even possible to build computers sufficiently powerful, assuming that technological advances do not slow. The world’s most powerful supercomputers can currently simulate around 10,000 of the brain’s 100 billion nerve cells at the maximum level of biological detail. And that is as far as the technology will go.

The problem is that the brain is an expert in doing many different things at once. The brain constantly performs masses of calculations in parallel, unlike computers which like to do one calculation at a time. “The brain uses incredibly small amounts of energy given how much information it processes,” Anders Lansner says.

“Our computer simulations are much less energy-efficient.”

When the brain is active, it needs about 20W of energy, which is about the same as a low-wattage light bulb. But no computer would be able to do the same thing without burning up.

Scientists at the SBI are working on detailed simulation of activity in what is known as a cortical column – a functional unit of the cerebral cortex consisting of around 10,000 densely packed nerve cells. A cortical column is approximately half a millimetre across and two millimetres long, and handles as much information as an advanced computer. By combining many such models, the scientists then want to simulate activity in a larger part of the cortex, which is necessary to understand how different parts of it work together to carry out a task.

Limitations in computer power can always be compensated for by reducing the level of detail in the models. With a slightly lesser level of detail, researchers have already been able to simulate activity in a couple of square centimetres of the cerebral cortex, containing more than 20 million nerve cells and 10 billion synapses. By further reducing the level of detail, scientists at SBI can also simulate even more large-scale networks. It is then possible to study how entire systems in the brain interact. The suite of models under development can together give us an understanding of how molecular processes relate to various mental functions and disturbances in these functions.

“For example, we’ll be trying to find out what happens when we use willpower to override our emotional reflexes,” says Martin Ingvar. “Control over older brain functions in evolutionary terms sets us apart from most other animals and plays an important role in our social relations.”

The SBI’s supercomputer is also well-suited to producing images with PET technology. An ultramodern PET scanner has recently been installed which, with the help of the supercomputer, can be used to its full capacity.

“For example, we’ll be trying to find out what happens when we use willpower to override our emotional reflexes,” says Martin Ingvar. “Control over older brain functions in evolutionary terms sets us apart from most other animals and plays an important role in our social relations.”
The discovery of embryonic stem cells and ways of creating genetically modified mice has radically changed the basis for medical research. This is one reason why it was rewarded with the 2007 Nobel Prize in Physiology or Medicine.

**Knock-out mice revolutionise medical research**

In field after field – cancer, cardiovascular research, immunology and neurology to name a few – these discoveries have led to brand new understanding of normal biological development and disease processes. It has been more than 20 years since Mario R Capecchi, Martin J Evans and Oliver Smithies first presented their findings – how stem cells can be cultured, genetically modified and implanted into surrogate mothers who give birth to new generations of genetically modified mice.

Things have moved very quickly since then. Creating models where a particular gene is switched off – known as knock-out mice – makes it possible to work out what function that gene normally plays. So far more than 10,000 genes have been knocked out, and it will probably not be many years before the whole of the mouse's DNA has been examined. Just like humans, a mouse has around 22,400 genes, and these have been examined. Just like humans, a mouse has around 22,400 genes, and these have been examined.

Cardiovascular research is one of the fields where experiments with genetically modified mice have helped scientists to gain a more in-depth understanding, in this case of the mechanisms behind high blood pressure and atherosclerosis, which are among our most common diseases. Göran K Hansson, professor of experimental cardiovascular research at Karolinska Institutet, is one of the leaders in this field. He discovered that atherosclerosis is an inflammatory condition which develops when LDL (“bad cholesterol”) accumulates in the walls of blood vessels and triggers an immune response. The inflammation causes the plaques to break up, forming a blood clot which can give the patient a heart attack or stroke.

“We spent a long time working on blood and tissue samples from patients and found molecules that we thought were significant for the disease,” says Hansson, “but it was only through mouse models that we could confirm our hypotheses, namely that atherosclerosis is an inflammatory disease. With the help of the mice, we can now understand in depth which mechanisms control the development of the disease – for instance, which cytokines (signalling molecules) can slow or accelerate the disease.”

One of the first to produce his own knock-out mice was Christer Betsholtz, professor of vascular biology at Karolinska Institutet. Among other things, he is mapping how new blood vessels form and which mechanisms control this during normal biological development and in connection with diseases like cancer. Together with his team, he has developed around 30 different mouse strains with targeted genetic modifications.

“Blood vessels normally grow slowly and do not increase in either number or size,” he explains. “But sometimes this pattern is broken. With many tumour diseases, there is uncontrolled development of new blood vessels (angiogenesis) which supply the tumour with oxygen and nutrients. Changes in the blood vessels are also seen in some inflammatory diseases.”

While Betsholtz was studying the growth factor PDGF and its role, he discovered that without PDGF there is no formation of pericytes, a particular type of smooth muscle cell in the smallest blood vessels. These cells are essential for the formation of new blood vessels and for making them stable. This discovery marked a breakthrough in angiogenesis research. Betsholtz has subsequently been able to demonstrate with the help of his models that pericytes play a number of different roles, partly depending on the type of tumour in which they are found. This research has led to a number of attempts now being made to develop medicines which target these cells and PDGF.

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**Definitions**

**Transgenic mouse** – a new gene is added, resulting in over-expression of that gene.

**Knock-out mouse** – a gene is switched off, its function is knocked out.

**Knock-in mouse** – a defect in the mouse's genes is activated by adding a particular DNA sequence.
The 2007 Nobel Prize was awarded partly for a way of modifying a specific gene

Embryonic stem cells are cultured and treated so that one of their genes is modified

The genetic modification takes place when many copies of an artificially modified gene are added to the culture dish. An electrical pulse opens up the cells, and the new modified gene is introduced into the DNA of some of them.

The genetically modified cells are separated out and injected into an early mouse embryo, known as a blastocyst.

In the blastocyst, the genetically modified stem cells mix into a mosaic with the inner cell mass.

The surrogate mother gives birth to mice with a mosaic of cells - a mixture of normal and genetically modified cells.

Mice with the modified genes in some of their cells are crossed with ordinary mice. After a few crosses, mice are born which carry a single copy of the modified gene. These mice are paired with one another, and some of their offspring will carry two copies of the modified gene.

Knock-out mice, as these mice are called in cases where the genetic modification means that they are missing a specific gene, can be used as experimental animals to conduct research not only into diseases and their treatment but also into the role of genes in both health and disease.
Nobel facts

The winners of the Nobel Prize in Physiology or Medicine are appointed by the Nobel Assembly at Karolinska Institutet, which consists of 50 professors from the institution.

All nominations, investigations and discussions leading to the award of the prize are kept confidential for 50 years.

The prize money is currently SEK 10 million. When the first prize was awarded in 1901, the prize money was SEK 150,000.

Of the 189 winners of the Nobel Prize in Physiology or Medicine, only seven have been women.

Almost all of the winners have done their work in Europe or the USA.

The discoveries of penicillin and the DNA double helix are two examples of key breakthroughs rewarded with the Nobel Prize. The discovery of X-rays was rewarded with the Nobel Prize in Physics in 1901 but has been of enormous importance for medical research as well.

Two prizes which have come in for criticism from an ethical perspective are the 1949 prize for lobotomy as a therapy and the 1948 prize for DDT, a pesticide which later turned out to poison the environment.

The Nobel Prize in Physiology or Medicine is awarded to individuals who have made significant contributions to medical science. The winners are chosen by 50 professors at Karolinska Institutet. The Nobel Assembly at Karolinska Institutet appoints these professors to realise his plans. Karolinska Institutet did not believe that it had sufficient resources and was reluctant to take on the role at first. Over a century later, though, this responsibility is shouldered with pride.

Alfred Nobel’s will was first opened – especially not those who had been appointed to realise his plans. Karolinska Institutet did not believe that it had sufficient resources and was reluctant to take on the role at first. Over a century later, though, this responsibility is shouldered with pride.

But nobody was applauding when Alfred Nobel’s will was first opened – especially not those who had been appointed to realise his plans. Karolinska Institutet did not believe that it had sufficient resources and was reluctant to take on the role at first. Over a century later, though, this responsibility is shouldered with pride.

What actually is an important medical discovery which benefits mankind? This is the question which Karolinska Institutet’s Nobel Assembly has to answer.

Long way to Nobel Prize

“Nobel didn’t give us much guidance,” says Hans Jörnvall, secretary to the Nobel Assembly at Karolinska Institutet, “but he did write that what is to be rewarded in medicine is discoveries and nothing else. We don’t award the Nobel Prize for lots of small advances or for long and faithful service.”

No, to win the Nobel Prize you need to revolutionise accepted thinking and take medical science a giant leap forwards. Then you have to get the international scientific community to acknowledge the greatness of your discovery so that they put you forward as a candidate. Last, but not least, it needs to convince the Nobel Assembly at Karolinska Institutet – the 50 professors who ultimately decide the Nobel Prize winners.

The Nobel Prize has been awarded for more than a century now. Will there ever be a shortage of important discoveries to reward?

“No, we don’t think so,” says Jörnvall. “For a while, when the human genome was being mapped, many thought it was all over, that we now knew practically everything there was to know. But they thought the same in 1907 when they discovered new cells, and will probably feel the same way again in 2107.”

The hardest thing, he says, is not finding major discoveries, but identifying the individuals behind them.

“Research is increasingly collaborative, and often many different people are involved. Our job is to find out who did what. Sometimes it’s so hard that we can’t find all of the answers, and so another discovery is rewarded instead.”

Anders Bárány, deputy director of the Nobel Museum, thinks that the 2007 Nobel Prize in Physiology or Medicine is a fairly typical and fully deserved example. It is rare for the Nobel Assembly’s decisions to encounter protest, although some prizes have come to be questioned with hindsight.

“There is at least one prize which was quite clearly wrong, namely the 1926 prize awarded to Johannes Fibiger,” says Bárány. “He won the prize because he was believed to have shown that stomach cancer can be caused by a parasite in cockroaches, but this is not believed today.”

But most prizes stand the test of time, and some of them still shine particularly strongly, such as the 1962 prize to Crick, Watson and Wilkins for the discovery of the DNA double helix. And the Nobel Prize has become more and more prestigious over the years.

“Its success has to do with the size of the prize money and the great care with which the winners are chosen,” says Bárány. “It’s also significant that the winners get to come to Stockholm and meet the royal family. Many of them have been very taken with that.”
Bengt Samuelsson, professor emeritus at Karolinska Institutet, was awarded the Nobel Prize in Physiology or Medicine in 1982 together with Sune Bergström and John Vane for their discovery of prostaglandins and the closely related leukotrienes. He talks here about what the prize has meant both for him personally and for people in general.

Text Cecilia Odlind

From bow wave to brain wave

Was there a real Eureka moment when the big discovery was made?
– I was out sailing with my family in the Stockholm archipelago when I woke up one Sunday morning on a small island and suddenly realised how substances formed in asthma were related to molecules we’d discovered a few months earlier. Within a few weeks we were able to determine the structures of these substances, leukotrienes, which scientists had been after for forty years.

Were you surprised when you learned that you’d won the prize?
– Of course. My wife and I were in Boston to take part in the celebrations of Harvard Medical School’s 250th anniversary. Due to the time difference, I was asleep when the secretary to the Nobel Committee called to give me the good news. The phone never stopped ringing after that.

What has your discovery meant for people in general?
– Our knowledge of these substances has been, and will remain, very important in the development of new medicines. For example, the everyday painkillers aspirin and ibuprofen work by blocking the formation of these substances. Prostaglandins are also used as medicines themselves in the treatment of glaucoma and to induce childbirth. The discovery has also led to new asthma drugs.

What are your top tips for someone wanting to win the Nobel Prize?
– Start researching as soon as you can! The choice of research field is also crucial. It’s important to work on problems which are not only interesting but also researchable in the sense that there are suitable
methods for approaching them. It’s good to combine different disciplines, such as chemistry or physics with biology. You also need to discover something new – the Nobel Prize is awarded for discoveries, not for long and faithful service. The choice of supervisors and colleagues is also important. My first supervisor was Sune Bergström, with whom I later shared the prize. He, in turn, received the first prostaglandin preparations from previous Nobel Prize winner Ulf von Euler, who encouraged him to try to determine their structure. Sune Bergström was then working in Nobel Prize winner Hugo Theorell’s department. My second supervisor was E J Corey at Harvard University, who won the Nobel Prize in Chemistry in 1990.

What qualities are important for success as a scientist?

– An enquiring mind is important, but so are energy and perseverance, as discoveries are often the result of long-term research. Discovering something new about, say, how the human body works, something which nobody previously had any idea about, is an amazing feeling. It’s an unbeatable motivator, especially if the discovery means that diseases can be cured and human suffering reduced.«

Bengt Samuelsson’s top tips for budding Nobel Prize winners

• Start researching as early as possible
• Work on problems which are researchable
• Try to combine different disciplines, such as chemistry or physics with biology
• Discover something new – nobody wins the Nobel Prize for long service alone
• Get a past Nobel Prize winner on board as your supervisor or tutor
• Be inquisitive, energetic and perseverant

Discovering something new about, say, how the human body works, something which nobody previously had any idea about, is an amazing feeling. It’s an unbeatable motivator, especially if the discovery means that diseases can be cured and human suffering reduced.«

Has there been a downside to winning the Nobel Prize?

– As long as you have the good sense to turn down irrelevant invitations to give talks and be an “expert”, then I don’t see any particular problems.

What did you do with the money?

– I invested it in shares, although some of it did go towards some slightly better wines to go with dinner.

What do you think about the 2007 prize?

– Brilliant! Their research into embryonic stem cells and ways of switching off particular genes in laboratory animals, such as knockout mice, has given scientists new opportunities to understand individual genes and the function of gene products. This has been very important in the development of new medicines.
At the beginning of the 1980s the World Health Organisation (WHO) initiated a special programme to reduce child mortality caused by diarrhoeal diseases. It was estimated that around two-thirds of all deaths from diarrhoea were due to acute watery diarrhoea and acute dehydration. The focus would therefore be on promoting the use of oral rehydration therapy – solutions containing sugar and salts. Pre-packaged powders which could easily be dissolved in water and given to children to drink were distributed. All sick children were also to be given increased amounts to drink in order to compensate for the severe fluid loss. These recommendations were incorporated into most countries' national health programmes, and active information campaigns were run through the WHO, UNICEF and national authorities.

In parallel with this, there were improvements in access to clean water and sanitary conditions – factors known to reduce the incidence of diarrhoea.

So what was the outcome? Mortality from diarrhoea among children is believed to have fallen, but an estimated two million children still die from it every year in poor countries – and virtually no children at all in rich countries. And no studies have been able to demonstrate any real decrease in the incidence of diarrhoea in low-income countries.

Birger Forsberg, who is currently conducting research at Karolinska Institutet, worked for the WHO in the mid-1980s when there were very high hopes for the diarrhoea programme.
To understand all this, we need to have more knowledge and also be very aware of people’s everyday circumstances.

“I never thought that things would look like this today,” he says.

Together with other researchers at Karolinska Institutet and the Nordic School of Public Health, he has reviewed data from a large number of health surveys from 40 low- and middle-income countries. In these surveys, mothers were asked how they treated their children when they had diarrhoea – whether they gave them special rehydration solutions, extra fluids or neither. The results, published in the WHO Bulletin in 2007, show that the use of rehydration solutions and increased fluids has increased, but only very slightly and slowly. The study estimates that, even today, 307 million children go without rehydration solutions when they suffer from diarrhoea, 356 million do not receive extra fluids, and 227 million receive neither. It is therefore unclear why global studies have been able to show a significant decrease in child mortality from diarrhoea during the same period.

What could be the reason why an international campaign on this scale has failed to have the desired impact? The researchers point to a number of possible explanations. Perhaps the information was not distributed or emphasised sufficiently to all households concerned. Perhaps there are conflicts of interest in some parts of the care chain. Other studies have shown that women with more education are more likely to take on board advice on treating children with diarrhoea. It is also known that caregivers who are in contact with local health services give their children better treatment.

“Because of this, we need to have more knowledge and also be very aware of people’s everyday circumstances,” says Birger Forsberg.

It is possible that a family with limited resources will not be able to look after a sick child sufficiently well even if the knowledge is there. Giving fluids to a child with severe diarrhoea can be a continuous process around the clock in the most acute phase. In households with limited resources, this may take second place to other important activities. Treatment with fluids can also be seen as ineffective and unrewarding, as it does not put an immediate end to the diarrhoea itself but primarily protects the child against more severe symptoms. Many ask for antibiotics or antidiarrhoeal medication instead.

It also has to be remembered that diarrhoea is as common in children in many areas as a runny nose is in children in Sweden. Parents therefore react more to the child’s general state of health than to the diarrhoea itself, which may mean that treatment is often begun on the late side.

Birger Forsberg has conducted further research into developments in diarrhoeal diseases, including in Ceará, a state in north-eastern Brazil, where child mortality from diarrhoea is reported to have fallen in recent decades. The aim of the study there was to clarify whether this was due to decreased incidence, improved treatment or both. Living standards in this area have
risen since the 1980s, and several factors which could contribute to a reduced incidence of diarrhoea have improved. These include water quality, toilets, waste collection, incomes, literacy, primary care and vaccination. The study shows that the differences in incidence between different parts of the state cannot be attributed to any single factor.

“It’s probably the overall raising of living standards which has led to the reduction in disease,” says Forsberg. “Health is a complex issue, and often difficult to explain on the basis of individual factors. It’s the overall development and the interaction between all of the risk and health factors which lead to health improvements. This argument may apply to both morbidity and mortality.”

Future research in the area will include the use of qualitative methods to try to capture how people out in the community view diarrhoea and its development. There is a widespread view among elderly people that diarrhoeal diseases have decreased in importance in Brazil. What is the reason for this view? How do people themselves explain the changes they have seen? And how does the reality which people describe tie in with data from the health care sector and studies of diarrhoea? The answers may provide interesting information which can take our knowledge about the determinants of ill-health forward.

Diarrhoea is still behind a fifth of the ten million deaths among children below the age of five reported each year in low- and middle-income countries.

“It is evident that a huge effort is still required to improve the care of children with diarrhoea and reduce child mortality from diarrhoeal diseases,” says Forsberg.

Publication:
Diarrhoea case management in low- and middle-income countries – an unfinished agenda
Forsberg BC, Petzold MG, Tomson G, Allebeck P.
Link: http://www.who.int/bulletin/volumes/85/1/06-030866.pdf
The complete human genome has been examined in a search for the genes that lie behind rheumatoid arthritis. The results confirm previous hypotheses, and throw the focus onto previously unsuspected genes.

Rheumatoid arthritis is the most common arthritic disease, affecting approximately 1 per cent of the population. The causes of the condition are unknown, but scientists believe that the risk of developing it depend approximately equally on genetic factors and on environmental and lifestyle factors. An international research project led by professors Lars Klareskog and Lars Alfredsson from Karolinska Institutet, in collaboration with research groups in the US and Singapore, has compared the genetic material of just over 1,500 sufferers of rheumatic arthritis with that of 1,850 healthy control subjects. The results show that the genetic material of those with rheumatoid arthritis differs from that of the control group in three locations: two genes that had previously been associated with the disease, and a third gene complex known as TRAF-C5, which had not previously been examined. The Swedish and American research groups have used the same material to examine the significance of one particular region in the genetic material. The results revealed that a further gene, STAT4, is associated with rheumatoid arthritis.

“It’s exciting that we have discovered individual genes that affect the risk of contracting the disease,” says Lars Klareskog, “but the most important aspect is that the results provide us with a broader basis for understanding the mechanisms that play a role in the initiation and progress of the disease. The two most important genes had already been discovered, and this means that we are on the right track”, he concludes.

The projects are examples of a growing trend in genetic research: large-scale international collaboration. Sweden’s unique patient registers are used for the collection of samples and the analysis of the interaction between genes and environmental factors, while the genetic analysis is carried out in Singapore, using state-of-the-art modern technology.

“We are working intensively with the collaboration with Singapore, since this is a country that is currently investing aggressively in biological sciences and biotechnology. This is the second joint project with Singapore that has been highly successful”, says Jan Carlstedt-Duke, dean of research at Karolinska Institutet.

Publication:
TRAF1-C5 as a risk Locus for rheumatoid arthritis; A genomewide study
STAT4 and risk of rheumatoid arthritis and systemic lupus erythematosus

Genetic analysis helps scientists to understand the origin of rheumatoid arthritis.
A newly discovered gene that increases the risk of developing MS

A previously unknown gene has recently been identified that increases the risk of developing multiple sclerosis, MS. This is the first newly discovered MS gene for 30 years.

“The gene plays an important role in the function of the immune response”, says professor Jan Hillert from the Karolinska Institutet. He leads one of the two research groups – one Swedish, one American – that lie behind the discovery.

The link between MS and a gene on chromosome 6 has for a long time been the only known genetic factor for MS. Now, however, strong evidence of an association between MS and a gene on chromosome 5 was published last summer. “The discovery provides further evidence that MS is an autoimmune disease, in which the body’s own immune response attacks the nervous system”, says Jan Hillert.

“This is important, since the medicines against MS that are currently used are based on the assumption that the disease is an autoimmune disease. Knowledge that confirms this assumption gives us the confidence needed to continue to use and develop these medicines, which alleviate the autoimmune response”, he continues.

The newly discovered gene, IL7R, codes for the receptor for an important signal substance in the immune system. This substance is particularly important in the function of one particular type of white blood cell, T-cells. We do not know exactly how this gene increases the risk of developing MS. It may cause an imbalance between the T-cells that stimulate inflammation and those that inhibit it.

Professor Hillert’s group has recently published an article in the journal PLoS One describing a study showing that the gene that was previously known to be associated with an increased risk of developing MS, HLA-DRB1, has a neighbour, HLA-A, that also influences the risk of developing MS.

“This means that more parts of the immune system than previously believed are involved”, says Jan Hillert.

Publications:
- Variation in interleukin 7 receptor alpha chain (IL7R) influences risk of multiple sclerosis
- HLA-A Confers an HLA-DRB1 Independent Influence on the Risk of Multiple Sclerosis

Nitrogen oxide lowers blood pressure

A food supplement containing sodium nitrate has been shown to have a beneficial effect on blood pressure. The nitrate is converted during digestion to nitrogen oxide, which is a key component in the body’s normal regulation of the vascular system.

Several healthy volunteers were given a food additive corresponding to the amount of nitrate present in 150-250 g nitrate-rich vegetables for three days. The diastolic blood pressure of these subjects decreased significantly, while that of a control group did not. In contrast, the systolic blood pressure and pulse rate were not affected.

It has previously been established that a diet rich in fruit and vegetables decreases blood pressure, but it has not been possible to identify any one component. The detailed mechanism by which the nitrate lowers blood pressure now needs to be determined.

Publication:
- Effects of dietary nitrate on blood pressure in healthy volunteers
  Larsen FJ, Ekblom B, Sahlín K, Lundberg JO, Weitzberg E.
A previously unknown mechanism of insulin release

Scientists at Karolinska Institutet have discovered a previously unknown mechanism by which beta cells in the pancreas release insulin into the blood, when this is required. The discovery may be of major significance in the treatment of diabetes and the complications that accompany the disease.

Insulin is a hormone in the body that regulates the blood sugar level. Type 2 diabetes arises when beta cells can no longer release sufficient insulin to compensate for the insensitivity to insulin that is present in the body.

The newly discovered mechanism involves a molecule known as InsP7. Scientists at Karolinska Institutet have shown that InsP7 is an important signal molecule in regulating the release of insulin.

“This discovery raises the hope of developing new drugs against diabetes”, says Per-Olof Berggren, professor at Karolinska Institutet and, in collaboration with associate professor Christopher Barker, leader of the study.

Previous research has described a Japanese family with a hereditary disposition to type 2 diabetes, in which the gene that regulates the formation of InsP7 in beta cells is mutated in the majority of the family members. Mice that lack this gene also display many of the defects that characterise human diabetes.

“The signal pathway that we have mapped in the beta cells may be of major strategic importance in our attempts to understand and treat diabetes”, says Per-Olof Berggren.

The same research group has also thrown light on an old mystery – how can insulin-producing cells maintain exactly the right number of copies of particular types of important proteins in their outer membranes? Proteins known as KATP-proteins are components of the ion channels in the cell. These channels are positioned on the surface of insulin-releasing cells and transport potassium ions, in a process that is regulated by ATP. Their position in the outer membrane enables them to monitor the blood sugar level, and control insulin release. It has previously been unclear how the insulin-releasing cells can maintain exactly the right number of KATP-channels on the cell surface. Scientists at Karolinska Institutet have discovered a previously unknown mechanism by which the sugar stimulates the KATP-proteins to take up the correct positions in the cell surface.

Publikationer:
Requirement of inositol pyrophosphates for full exocytotic in pancreatic beta cells
Glucose recruits K-ATP channels via non-insulin-containing dense-core granules

A simple stool sample makes colonoscopy unnecessary

Children with suspected colorectal inflammation usually have to undergo an unpleasant colonoscopy – an optical investigation of the intestine – while under general anaesthesia. A recent doctoral thesis published at Karolinska Institutet shows that a simple stool sample can be just as effective for diagnosis.

IBD (inflammatory bowel disease) is the name of a group of diseases that affect the mucous membranes of the gastro-intestinal tract. Crohn’s disease and ulcerative colitis are the most common of these diseases. It can be difficult to distinguish between IBD and other conditions, such as the less serious IBS (irritable bowel syn-
Controlling energy production in the cell

In order for the body to be able to keep warm, move around and, indeed, survive, the mitochondria – the power stations of the cell – must release the correct amounts of energy. Scientists at the Karolinska Institutet have discovered how the mitochondria prevent the cell from overheating.

Mitochondria release energy in a process known as oxidative phosphorylation – a chemical process in the mitochondria in which the cell’s energy currency – molecules of ATP – is formed. Important components of the oxidative phosphorylation pathway are coded for by the mitochondrial DNA – mtDNA – and thus the cell can adapt its production of energy as required by increasing or decreasing the expression of mtDNA. However, detailed knowledge of how this regulation takes place is scarce.

Two research groups at Karolinska Institutet, led by Claes Gustafsson and Nils-Göran Larsson, respectively, have now made a major breakthrough: the discovery of a previously unknown transcription factor, MTERF3. This factor inhibits the expression of mtDNA, and it can thus slow energy production in the cell.

The discovery has been published in the journal Cell, and may lead to new possibilities for the treatment of serious diseases. Impaired mitochondrial function causes an energy supply crisis in the cell, and this probably plays a major role in several endemic diseases, such as diabetes, heart failure and Parkinson’s disease. It plays a role also in the normal process of aging.

Publikation:

MTERF3 is a negative regulator of mammalian mtDNA transcription


Palnsk 2007ok:07-12 diabetes5.0 08-04-30 12.58 Sida 37
Your teeth reveal

Periodontal disease is one of our big public health problems, and more and more studies are showing a link between periodontal disease and other big public health problems, including cardiovascular disease and diabetes.

Swedes generally have good dental health, but more than 20 per cent of adults nevertheless suffer from periodontal disease – advanced gum disease. Periodontal disease can therefore be said to be one of Sweden's biggest public health problems.

Periodontal disease is an infectious disease where bacteria on the surface of the teeth trigger an inflammatory reaction in neighbouring tissue, which gradually becomes ulcerous and breaks down. Early signs of periodontal disease are inflammation of the gums and deep tooth pockets. Most cases can be treated very successfully, and the disease is both prevented and treated by good oral hygiene to keep the surfaces of the teeth clean.

Several studies under way at Karolinska Institutet are looking at the links between oral health and some of the most common public health problems in Sweden, above all cardiovascular disease. This is a red-hot research field, and Sweden is a front-runner internationally. One study which has attracted considerable attention concerns oral health and its connection with premature death. The lead author of the study is Birgitta Söder, professor of odontological prophylaxis at Karolinska Institutet. She tested a large group of people aged 30–40 who were divided into two groups: one with periodontal disease but no known cardiovascular disease, and the other, the control group, with neither. Their oral health was first investigated in 1985 and then followed up in 2001. It was when the researchers began to look at the general state of health of the people in these groups that the connection between periodontal disease and premature death emerged.

“When we compared this population with the Swedish Cancer Register and the Swedish Cause of Death Register, we found to our great surprise that those who
had lost a molar due to periodontal disease were more likely to die prematurely,” says Söder.

It emerged that the risk of dying prematurely – on average at the age of 47 – was 3.6 times higher among those who had periodontal disease. The causes of death were cancer, cardiovascular disease and diseases of the gastro-intestinal system.

“In the study, we saw a big difference between patients with periodontal disease and healthy people when we looked at changes in the walls of the carotid artery,” she says. “Those with periodontal disease were more likely to have early signs of atherosclerosis – hardening of the artery walls.”

Another surprise in the study was that periodontal disease was a bigger risk factor than smoking in terms of premature death from the diseases studied.

“Naturally smoking is a huge risk factor for cardiovascular disease – this is well-established – but now we can add periodontal disease as another big risk marker,” says Söder.

The link is therefore clear, but the cause has yet to be found. What is it that makes periodontal disease correlate so closely with other public health problems? The probable reason is that periodontal disease is an inflammatory disorder caused by specific bacteria. It develops quietly and surreptitiously over many years, maybe even decades, before it is discovered and treated. This means that the body has suffered from low-intensity inflammation for a long period, constantly triggering our immune system into forming antibodies to the bacteria in question.

Anders Gustafsson, professor of periodontology at Karolinska Institutet, and his research group have looked at the link between periodontal and cardiovascular disease in women, an understudied group in these contexts. We know that women often have different and more diffuse symptoms than men following a heart attack, for example, and so they wanted to see if there were any differences in this context. However, it emerged that the connection between periodontal and cardiovascular disease looks the same in both women and men: the women who had had a heart attack had more deep tooth pockets and fewer remaining teeth – in other words, poorer dental health – than the healthy women in the control group.

There is often a hereditary component in the development of disease. This can be ruled out by studying identical twins, who have the exact same genetic make-up. This was done by researchers Farnaz Tabrizi and Kåre Buhlin, who are part of the same research group as Anders Gustafsson. They looked at ten pairs of identical twins, of whom one suffered from cardiovascular disease and the other did not.

“The ones with cardiovascular disease had much worse periodontal disease than their healthy twins, and this was clear even though only ten pairs were included in the study,” says Gustafsson.

It is difficult to study the causal relationships in an ethically acceptable way. Ideally, one would want to conduct a large study where half of the subjects undergo careful treatment of their periodontal disease and the other half receive no treatment at all, and then see which group has the most heart attacks.

“This is entirely impossible for ethical reasons, so instead we have to look at surrogate markers for cardiovascular disease in blood samples,” explains Gustafsson.

Surrogate markers reveal the presence of various diseases and might be levels of cholesterol, blood sugar, antibodies or inflammatory factors such as CRP, known as acute-phase proteins. If we can alter these levels by treating periodontal disease, this would be a good indicator of how periodontal disease impacts on the development of other diseases. Anders Gustafsson and his colleagues are now performing an intervention study where 70 patients with serious periodontal disease but no cardiovascular diagnosis receive treatment for periodontal disease and then give blood samples every three months. The results show that CRP levels fell after treatment and were still lower than before after one year. The study has been reported at several congresses but has not yet been published and so has not yet been peer-reviewed.

What is the clinical significance of these research findings? None as yet, as the level of knowledge is not sufficient. But if there does turn out to be a clear causal connection, this could have considerable clinical significance for both dentistry and cardiology.

“We cannot say that brushing your teeth reduces the risk of cardiovascular disease, as that study has yet to be performed,” says Gustafsson.

To increase knowledge about the causal relationship, he is calling for larger and more specific studies to analyse the effect that treatment for periodontal disease has on various different risk markers relating to cardiovascular disease. Birgitta Söder believes that her study of premature death can be interpreted such that you will live longer if you maintain good oral hygiene and do not develop periodontal disease. But she notes that there is a need for more studies to confirm this claim – studies which look in more detail at what particular types of cancer and combinations of bacteria are related to premature death, and whether there are differences between men and women.
A unique global research collaboration has shown that two common genetic variants affect the risk of breast cancer. The study is the largest ever of its kind and involved 15 research groups and almost 40,000 women.

Text Ola Danielsson

Unique collaboration identifies new breast cancer genes

Like many other types of cancer, breast cancer hits certain families harder than others. Although environment and lifestyle factors can play a role, there is no doubt that breast cancer has a significant hereditary component. Women whose close relatives have had the disease run double the risk of being affected, and some calculations suggest that the 12 per cent of women who are most susceptible genetically account for as many as half of all cases of breast cancer.

The Breast Cancer Association Consortium, bringing together 15 different research groups from all around the world, has now studied genetic susceptibility to breast cancer in a population of almost 40,000 women, with the result that two brand new genetic variants have been linked to the risk of developing breast cancer.

According to Per Hall and Sara Wedrén, researchers at Karolinska Institutet who have been working on the study, the study in itself is almost as unique as its results:

"The study is based on a unique collaboration and is the largest yet in breast cancer research. The results are important because it's the first time that scientists have conclusively identified genetic variants which affect the risk of breast cancer and are also very common in the population. One of the variants can be found in around a quarter of all European women."

This is a big difference compared to the "breast cancer genes" identified in the past, which have a major impact on the risk but are very uncommon in the population. In the 1990s it became known that women with mutations in \textit{BRCA1} and \textit{BRCA2}, the two most important and most well-known breast cancer genes, run a substantially increased risk of being affected by the disease. To identify the women most at risk, it has therefore become practice to look for these mutations in women from high-risk families. However, as mutations in \textit{BRCA1} and \textit{BRCA2}, as well as the other six known breast cancer genes, are very rare, they explain only a small part of the overall hereditary component. Only a few of the factors which cause the disease to run in families are known.

It has been very difficult to find other genes which can explain the rest of the hereditary component. The explanation is probably that the hereditary component is largely polygenic – in other words, it depends on the combined effect of a large number of genes. This insight has forced researchers to turn to new methods. So-called association studies are being performed in an attempt to show which genetic variants vary statistically in prevalence between sick and healthy women. But it has been hard to achieve unambiguous results with the limited data available. Because each gene has only a limited effect, the connection can only be revealed if the study population is very large.

The Breast Cancer Association Consortium was set up in 2005 to overcome this problem. It is a unique collaboration between 15 different research groups from all around the world who have pooled their data in order to carry out more effective studies. This has made it possible to use genetic information from almost 40,000 women in the largest association studies yet. These efforts have now resulted in two new genetic variants having been shown to be significant for the risk of breast cancer.

One of the two variants codes for a protein called caspase 8, whose role is to ensure that the body eliminates damaged cells which might otherwise be turned into cancer cells. The quarter of the European population who carry this genetic variant run a 10 per cent lower risk of developing breast cancer. The other gene, \textit{TGFB1}, results in a slightly elevated risk, although the connection in this case was weaker. It produces a growth factor which probably causes cells to proliferate and increases the risk of cells being turned into cancer cells.

Sara Wedrén stresses that the research
Breast cancer is the most common form of cancer among women worldwide. In Sweden, around one in ten women are affected at some time in their lives. Breast cancer is caused by a complex interaction of lifestyle factors, environment and individual susceptibility, in which the female sex hormones play an important role. These hormones affect the development of mammary cells and are also significant in the development of breast cancer. The risk of breast cancer is higher among those who have their first period at an early age and those whose periods end at a late age. It is also known that long-term oestrogen treatment in connection with the menopause results in a moderately increased risk of breast cancer.

The idea of this research is to get better at identifying risk groups. Most people run a very small risk of being affected and do not need any preventive treatment. But if we could learn how to pick up the most susceptible women before they fall ill, we’d be able to prevent a large proportion of deaths from breast cancer.

The consortium is currently identifying further genes associated with breast cancer, and new results have just been completed. According to Per Hall and Sara Wedrén, the big challenge in the future is studying how risk factors such as childbirth and breast-feeding affect women with a particular genetic profile. It is hoped that this can be studied on a large Swedish population within a few years.
International relief efforts have often been sent to a disaster zone without properly assessing the needs of the population. This is highlighted in the first academic thesis in Sweden to study the use of needs assessment for international health assistance following disasters.

Text Ulla Bredberg

Relief efforts do not always reflect needs

It is important to assess the needs of the population affected before aid is sent to a disaster zone. Here are some illustrative examples from Johan von Schreeb’s thesis.

No need to send food which is already there

A school in Beslan in Russia was attacked by terrorists in 2004. 329 people died from explosions and almost 700 were injured, many of them seriously. Four hospitals lay within 20 minutes’ drive of the school, with 2,500 beds and 900 doctors between them. This is 70 per cent more doctors per capita than in Sweden! The acute surgical care provided was satisfactory, and mortality would probably not have been any different if a similar drama had hit a suburb of Stockholm. Yet many countries sent medical equipment, medicines and food. But there was just no need for international medical assistance in Beslan.

Need for transport, not health care

During the low-intensity conflict in Palestinian areas in 2002, the situation was portrayed as if there were a need for medicines, equipment and international health workers.

“My study indicated that there was not yet any major effect on the public health situation, while the main problem for the population was the lack of free movement caused by road blocks,” says Johan von Schreeb. “This made it difficult to reach health care facilities when there was a need. It would have been more appropriate to have international humanitarian aid focus on helping with transportation rather than sending medicines and doctors.”

Life-saving care arrives too late

Following the four natural disasters which occurred in Bam in Iran in 2003, Haiti in 2004, Aceh in Indonesia in 2004, and Kashmir in Pakistan in 2005, a total of 43 international field hospitals were dispatched. None of them got there within the first 48 hours, which is the period when lives can still be saved. Despite this, these hospitals focused on life-saving trauma care, rather than the needs which dominate after a few days, namely normal hospital care.

“It seems to be an illusion that intercontinental transportation of field hospitals can save the lives of the injured,” says von Schreeb. “But field hospitals from neighbouring countries could potentially do this, and so acute emergency aid should be organised regionally.”

A disaster can be sudden or slow. When it affects a low-income country, there is often a shortage of resources, and international humanitarian aid is needed to help those affected. This assistance should focus on the five basic needs: water and sanitation, food, shelter, health care, and security.

Johan von Schreeb has studied the use of needs assessment for international medical relief after a number of disasters occurring since 2002, and has also studied to what extent assistance was adapted to needs. The results show that international aid has all too often been sent to disaster zones without a proper needs assessment beforehand.

To be able to perform a proper needs assessment and deploy the right relief efforts, there is a need for access to good information about the disaster and the context, including information about the area affected, the size and economic status of the country affected, and the resources available locally and regionally. International donors of humanitarian aid have jointly decided to distribute money on the basis of the needs of the population affected. There are well-described methods for conducting needs assessments, but the results of these assessments are applied all too rarely. Johan von Schreeb has studied the extent to which Sida – the Swedish International Development Cooperation Agency – used the results of needs assessments in its decisions to fund humanitarian health projects in 2003. Only a third of these decisions contained information on the size of the population to be assisted or other factors reflecting their health needs, such as mortality, malnutrition and access to water.

“I don’t interpret this as a critique of how Sida allocates money, but rather as a critique of the methodology used.”
Don’t panic!

Following the 2005 earthquake in Kashmir, von Schreeb was in the area as medical coordinator for Médicins Sans Frontières. The organisation was able to start providing medical assistance within a few days. Von Schreeb took the opportunity to test a new rapid assessment tool to gather population-based information on the needs of those affected. He interviewed a selection of those visiting health facilities about their situation and their immediate needs. A comprehensive study performed later, where everyone in the area was interviewed, showed that the early assessment painted a good picture of the situation, and that the estimation of mortality and the number of injured tallied well with the actual figures.

“The initial interviews gave a quick and accurate picture of what people actually needed – which, in this case, was mainly shelter against the cold winter.”

Abdullah Khan, a nurse from Kashmir, prepares for an operation in a provisional operating theatre.
Four Swedish issues of Medicinsk Vetenskap 2007.
The best articles are chosen for this English language edition of Medical Science.