DOPING info

Gene Doping

swiss olympic

Schweizerische Eidgenossenschaft
Confédération suisse
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Federal office of sports FOSPO

“But it only lives half as long”

Patients suffering from anaemia can be helped by a hormone that regulates the formation of red blood cells: erythropoietin, otherwise known as Epo. Athletes have also discovered the benefits of Epo – as a performance enhancer. That’s because if you have more red blood cells, you increase the amount of oxygen transported from the lungs to the muscles, which boosts endurance.

But Epo has many more effects, some of which are still not properly understood. To find out more, Max Gassmann has transferred the human Epo gene to mice. Their capacity to produce blood rose spectacularly. “Up to 25 per cent of their body weight is blood,” says Gassmann. “But it is as thick as liquid honey.” These mice show just what can happen when excessive amounts of Epo find their way into the organism. Iron-laced salts damage the kidneys, nerves suffer and muscles start to waste. The result: the animals only live half as long as normally.

“We bred a mouse with twice as many red blood cells”

Professor Max Gassmann
Institute of Veterinary Physiology,
University of Zurich

“Gene doping puts your life at risk”

Adolf Ogi
United Nations Special Adviser on Sport for Development and Peace

Medical research allows us to discover the genetic causes of diseases. This is why so-called gene therapies are being developed. But even before these therapies are available for patients, there are people longing to use gene transfer techniques to enhance sporting performances.

It is true that – unlike in science fiction stories – cloned super athletes will probably never make an appearance in our arenas. But that doesn’t mean that gene technology will not influence sport. Gene doping will become a reality much sooner than we think. Nobody knows if it is already being tested. One thing is sure though: these athletes – if you can call them that – are risking their lives. Because no researcher can say for sure what the long-term effects of gene doping will be on a healthy body.

Whether it will be very damaging or only slightly damaging should not even be discussed. Doping – be it chemical, hormone based or using genetic techniques – is not an option. Because sport is a wonderful activity, based mostly on an individual’s aptitudes. It allows us to measure up against one another and appreciate something together. Sport gives everyone the same opportunities. Poor or rich, black or white. For many of those living in underprivileged circumstances, sport gives them an opportunity to leave poverty behind. And for those who cannot tolerate one another, it’s a chance to find reconciliation in a fair competition.

Sport is a wonderful activity that brings people and nations closer together. We cannot let it become a battleground for unscrupulous human experimentation.

It’s all in your genes

The runner Roger Bannister, the first man to break the four-minute mile barrier in 1954, once famously said “athletes are not born equal”. For expressing what science has since shown to be true, he came in for hefty criticism because it was not politically correct.

We are not all the same. It’s obvious at first glance. There are differences in eye, hair and skin colour; our noses and heads have different shapes. These traits are inherited, as everyone knows. But they aren’t the only ones. There are boys and girls at school who run faster than the others without ever having trained. Some have strength and muscles; others have a slight build, even when they train.

In the sprint events, it’s almost always athletes with African origins that win. A dark-skinned athlete holds the world 100-metre record. At the last four Olympic Games, all the finalists in this event had west African origins. Almost the same can be said of the women. Over longer distances, it’s athletes with east African origins that dominate track events. But why aren’t there any Ethiopian weightlifters? Why do people from the Caucasus lack the endurance needed to win longer races, and why do almost no Asians engage in strength sports?

Because characteristics such as strength, speed, endurance or flexibility are to a certain extent inherited. Genes don’t just decide your skin colour, but also what kind of sport suits you best.

“I have an advantage”

Amaru Reto Schenkel
Swiss sprinter from Togo

I know that nature has given me a few characteristics that make me faster than others. But predisposition alone won’t make you a champion.

Why is there always a black person on the top of the podium at the end of the day? For a long time, there was a sort of “ghetto theory”. Dark-skinned people were supposed to be better at sport because of a lack of other opportunities to climb the social ladder. I think that’s rubbish.

First of all because there are sports where whites dominate, and secondly because I didn’t grow up in a ghetto, but in Switzerland. My origins are in the west African nation of Togo. The skeleton, muscles and metabolism of people there mean they are particularly suited to fast running. You could say we are born to be sprinters.

But predisposition won’t make a champion of you. Training and mental strength decide who wins and who loses. You have to empty your mind, and results will come. Even without doping. Because it’s not just cheating at sport, it’s cheating yourself.

Endurance in the genes

Eero Mäntyranta had – without knowing it – a genetic advantage for endurance sports. His body naturally produces more red blood cells than most people.

Eero Mäntyranta was a phenomenon. He won his first gold medal at the 1960 Winter Olympics in Squaw Valley with the cross-country relay team.

No one would have bet on the 23-year-old Finn becoming a champion. Eero is somewhat small for a cross-country specialist – just one metre 70 in his socks. But he took the 1964 and 1968 Olympics by storm, winning two gold medals, two silver and one bronze. He also took a few home from two world championships.

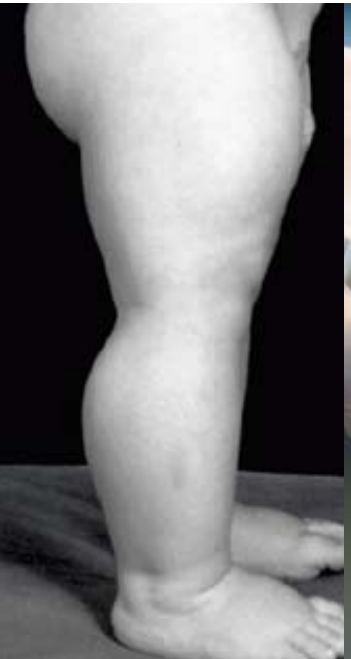
He was regularly suspected of relying on doping, something he always denied. It was only two decades later that his secret was revealed. Molecular biologists discovered he had a rare genetic mutation that helped his blood absorb large amounts of oxygen. Why? Because his metabolism was especially sensitive to Epo, the hormone that stimulates the production of red blood cells and is found naturally in the body.

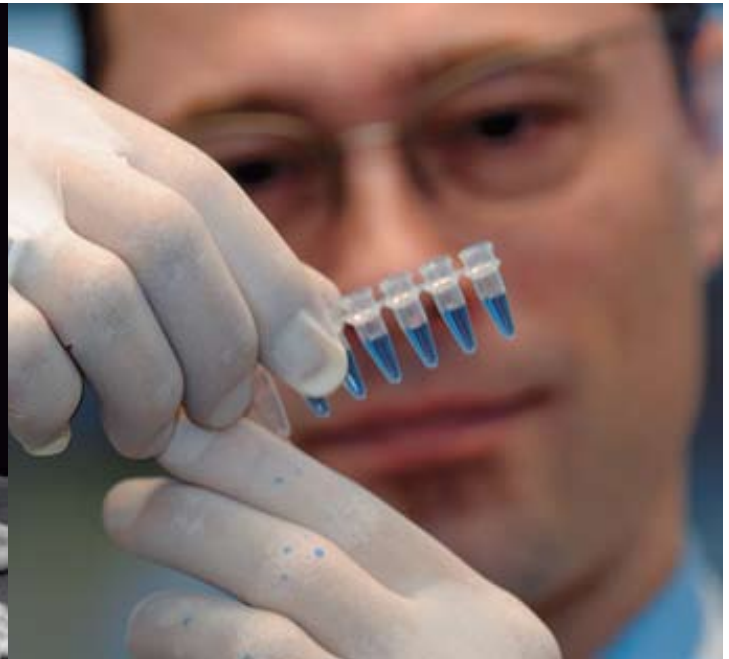
Mäntyranta had a natural advantage over his fellow competitors. He wasn't alone either: many of his relatives have the same mutation. So far, tests have detected around 200 people with it. Today, Mäntyranta lives in Lankojärvi, in northeastern Finland, where there is a museum dedicated to him as well as a monument.

Eero Antero Mäntyranta
Finnish cross-country skiing legend

Strength thanks to genes

Professor Markus Schülke
Paediatric Clinic, Neurology department,
Charité Hospital, Berlin





When Michael was four years old, he could hold two three-kilogramme dumbbells with his arms outstretched. A genetic mutation meant that his body was failing to produce myostatin, a hormone that limits muscle tissue growth.

Doctors were amazed when Michael* was born in 2000. The baby had muscles like no other. At first, they thought he was sick. But further investigation by paediatric neurologist Markus Schülke showed that the child was basically healthy. He inherited his muscles from his mother, who like many of her relatives, has a strong build. What made Michael special was a genetic mutation. His body produced no myostatin, which regulates muscle growth. "Myostatin is like a stop sign," says Schülke. "When it goes missing, the muscles stop their development later than usual." By the time Michael was four, he was twice as strong as children the same age. So far, there seems to be no negative effects for the youngster.

When Michael's case came to light, doctors began to dream of new therapies for people suffering from muscular diseases. Could the myostatin gene be switched off to help patients or the hormone's effects limited? Today, the early hopes have given way to reality. The latest research has shown that if muscles do grow in the absence of myostatin, extra strength does not increase in the same proportion. Twice as much muscle does not mean twice as much strength.

*Fictitious name.

Gene therapy

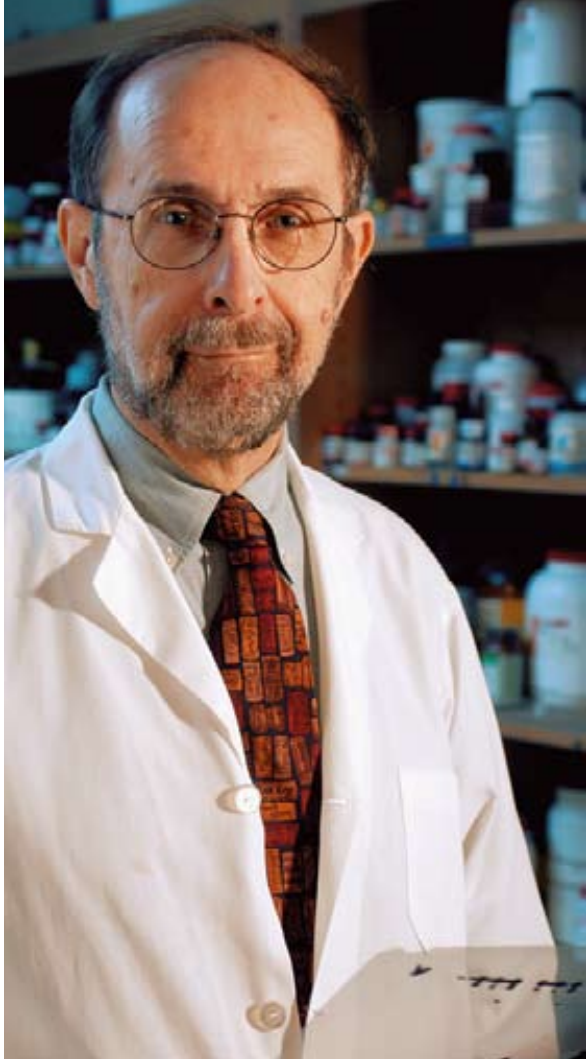
Gene therapy is still in its infancy, but we are optimistic that in the near future we will be able to cure many diseases with this technique.

Genes are made up of DNA, the blueprint that can be found in every cell of our body. Genes determine how proteins are put together, and these in turn control the functions of our body, such as hormone and blood cell production, or muscle growth. If a gene is defective or missing, the body cannot produce the right protein, and we fall ill. Medicine has great hopes that it can eventually cure diseases determined by genetics, by replacing sick or defective genes with healthy ones. You immediately think of diseases such as cancer or cardiovascular illnesses, but there are rarer inherited diseases such as immune deficiency or muscular atrophy.

It is difficult to ensure that a transplanted gene goes to the right place in the body to fulfil its function. One method is to use weakened viruses. Viruses replicate by injecting their genetic material into their victim's cells. However, we can modify their genetic makeup so they no longer transfer their disease-causing genes, but rather human ones that are missing in the patient.

Finding the right virus is not an easy task. You also have to be sure that enough of the replacement gene goes to the right place to take over its new function at the right time after receiving the right signal from the body. The wrong gene in the wrong place or a badly controlled one could have deadly consequences.

Since 1990, over 800 gene therapy trials involving more than 5000 patients have been performed. But only a few show good results. Children with immune deficiencies or certain types of cancer, for example, have responded to treatment. Doctors hope many other diseases will be added to the list of successes.



Professor Theodore Friedmann director of the gene therapy programme at the University of California San Diego and head of WADA's panel on gene doping.

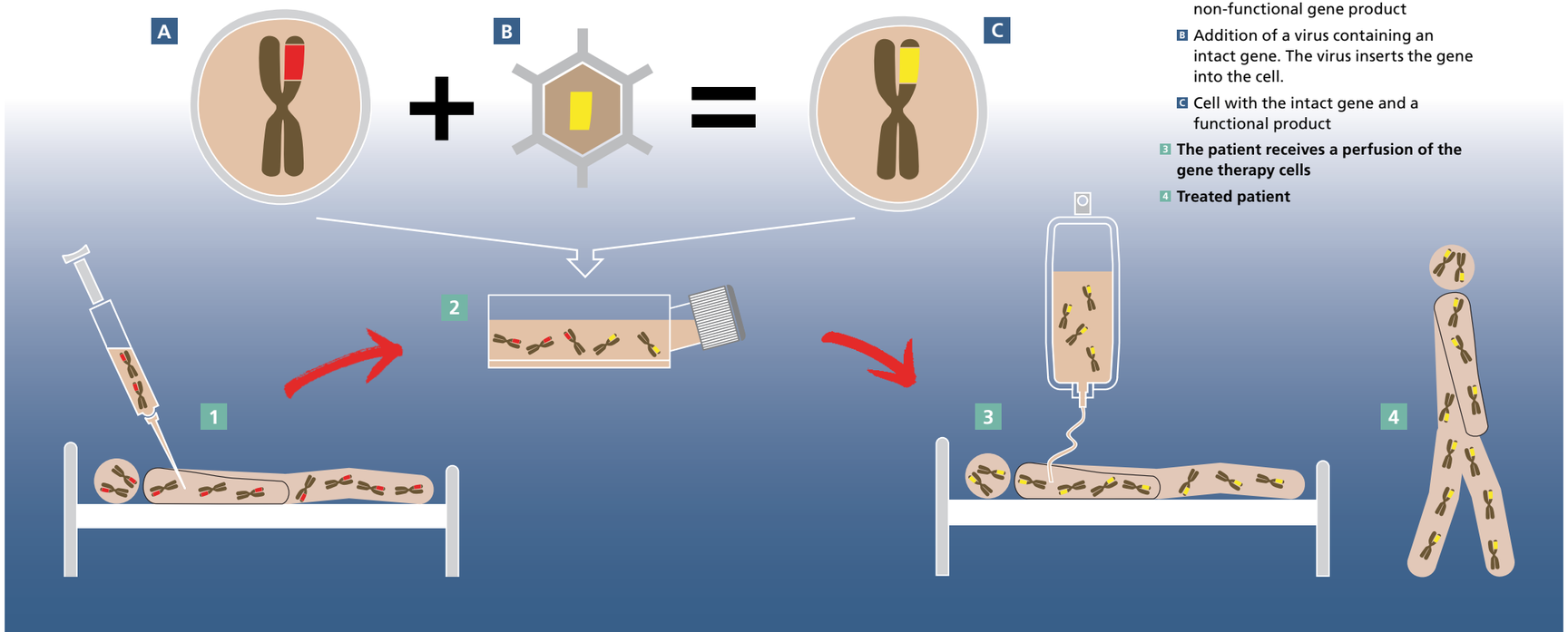
How gene therapy works

Genes used for medical treatment can be placed inside a virus which is then injected into the patient. But this is not by any means a reliable method. A better approach is to insert the genes directly inside the target cells – but outside of the body – using a so-called in vitro technique.

The most suitable cells are those that can be easily collected from the body and then transplanted back. These cells should also have a high life expectancy, ensuring that the genes remain active for a long time. Typical examples are white blood cells (T cells) or cells from bone marrow, which produce white and red blood cells. Muscle stem cells – so-called satellite cells – could be potentially used as well. However, even with very efficient methods of introducing normal genes into defective cells, there is no real assurance that the gene will function normally.

This type of treatment is known as "somatic gene therapy" since the cells used are drawn from the body and not related to the cells of the reproductive process (sperm and ova). In this way, genetic changes are restricted to the patient and cannot be passed on to any offspring. Germ-line gene therapy, which uses reproductive cells, has not been performed to date. It is controversial and often considered unethical, and has been banned in many countries.

GENE THERAPY



1. **Collection of cell material from the patient**
2. **Cell culture in a special flask**
   - A Cell with a defective gene and its non-functional gene product
   - B Addition of a virus containing an intact gene. The virus inserts the gene into the cell.
   - C Cell with the intact gene and a functional product
3. **The patient receives a perfusion of the gene therapy cells**
4. **Treated patient**

Sports genes

If injecting specific genes can cure diseases, shouldn't this technique be made available to everyone, even injured athletes? The jury is still out.

Scientists regularly publish lists of genes that could help improve sporting performances. In 2000, there were around 30 of these genes or variants of them. Today that figure has reached more than 150 and is still climbing.

The most potent "sports genes" affect erythropoietin (Epo) to improve endurance and myostatin to increase strength. But there are also growth factors such as IGF-1 or growth hormones (HGH). Recently, even a "Human Speed Gene" that boosts muscle performance was discovered. Genetics could also influence willpower, stamina and increase a person's pain threshold.

It would be very tantalising to improve athletes' performances in the long term by supplying them with these genes. Gene therapy would not make a champion out of a no-hoper, but a good athlete could become a super athlete with an injection of the right stuff. At least that's the theory of gene doping.

A remedy with risks and side effects

Severe side effects are rare in gene therapy when strict clinical conditions are respected and pure genetic material is used. What would the risks be if genes were illegally injected for doping purposes?

Clinical trials of gene therapy have so far proven to be generally safe. But there is some risk attached to these trials, as Jesse Gelsinger's case showed. The young American was born with a liver deficiency. That's why he decided to take part in a 1999 clinical study, and received a dose of genetically modified viruses delivered directly into his liver. His immune system put up a fight. Jesse was wracked with pain, feverish, his blood clotted and his organs collapsed. Just four days after the treatment, he was dead.

Other cases of gene therapy resulting in severe complications have been registered, either in clinical trials or in animal experimentation. In some cases, rapid death was the outcome; in others there were long-term consequences such as cancer, leukaemia or autoimmune disease.

It is rare for this to happen under strictly controlled clinical conditions and with pure genetic material. What nobody knows are the risks involved if gene therapy is applied for doping.

The long-term effects should not be underestimated. When an athlete stops using anabolic steroids, for example, their effect on muscle tissue stops as well. With genes that produce growth factors, there is simply no way of controlling them or shutting them down once they are in the organism. They could suddenly help tumours grow.

The effects of Epo will also stop quickly if usage is ended. But if someone received additional Epo genes, the blood cell count would remain high for life along with the increased risk of stroke or heart attack.

Professor Sandro Rusconi
University of Fribourg, Director of the National Research Programme "Somatic gene therapy"

Big muscles – big problems

The “Belgian Blue” cattle breed has a natural gene mutation that allows for so-called “double muscle” growth. But these animals also have huge problems.

Heightened performance thanks to modified genes is already a fact today. Thanks to a natural mutation of the myostatin gene, the “Belgian Blue” cattle breed has muscles like no other. They produce one third more meat than other breeds with hardly any fat. But while they are a producer’s dream, their lives are a nightmare. Many of them are sterile, and every second birth requires a caesarean section because the calf’s huge muscles cannot pass through the mother’s pelvic canal.

Since the case of a strong-muscled human baby was revealed in Berlin, trainers and athletes have been asking researchers if gene therapy could lead to bigger muscles. But have they asked cattle breeders about the side effects?

Taller … and sicker

Unilateral genetic selection can be dangerous, as the deaths of some particularly tall athletes have shown.

Flo Hymann was a volleyball star in the United States. She towered over her teammates at one metre 96, and could jump skywards like no other. But during a game on January 24, 1986, the machine ground to a halt. Flo’s legs started to shake. A few minutes later, she was dead. A burst coronary artery killed her.

It turned out that Flo was suffering from Marfan syndrome, an inherited condition that weakens the connective tissue. The coronary artery can therefore burst quite easily and the patient dies from internal bleeding.

This was far from an isolated case, as it happened to a number of American basketball players. All of the victims were especially tall, one of the characteristics of Marfan syndrome. Patients suffering from this problem are often very big, which tends to make them almost destined for some sports – so it seems.

These deaths have shown that selecting athletes because of a genetic advantage, for example body size, can also lead to the selection of genetic disadvantages, in this case weakness of the connective tissue.

Today, the NBA demands that every player undertake regular heart checks. But how would one keep an eye on genetically manipulated athletes?

Backyard doping laboratories

It is not particularly difficult to produce genetic material for doping purposes. To make it safe is much harder.

Producing genetic material is fairly simple. Raw material is cheap and can be legally purchased, and any biology student has the necessary knowledge. This means that illegal laboratories would have no trouble supplying material for gene doping.

But it could be far from pure. Or the virus used for the gene transfer could be more dangerous than the original virus. This represents a huge danger not just for the athlete, but also for all those taking part in the gene transfer.

Experimental gene therapy that has been carried out so far has been done under strict safety conditions and using the purest gene material. Patients were under close medical surveillance. But even then complications have happened – and people have died.

Who wants to take the risk of relying on gene doping material produced by a backyard laboratory?

Already a reality?

One trainer has already ended up in court for seeking a medication that could be used for gene doping. It hasn't been proven though that he gave it to any athletes.

Nobody knows if gene doping is being used right now. But a well-known German track trainer, Thomas Springstein, is suspected of having tried it. Investigators found suspicious e-mails on Springstein's computer asking for information about Repoxygen, a medication that had not undergone widespread clinical trials. It is supposed to help anaemic patients by anchoring the Epo gene in muscle cells and inducing Epo production. It would improve an athlete's endurance and is therefore banned under international doping rules. But its presence cannot be detected by doping tests.

At Springstein's trial, it wasn't possible to show he had actually purchased Repoxygen. Despite this, he was still sentenced to a prison term on probation. He had provided an underage female athlete with a testosterone preparation and investigators had found in his luggage many other substances that could be used for doping.

The investigator

Professor Bengt Saltin
Muscle research centre, University of Copenhagen

The law

Gene doping is already on the list of banned doping agents, even before being put to use.

The idea that genetically modified athletes will soon be appearing is somewhat alarming. This is why the World Anti-Doping Agency (WADA) convened leading personalities from sports and science for two conferences in 2002 and 2005 to discuss gene doping. Even if many questions remain unanswered, gene doping was prohibited. For the first time the WADA banned a certain type of doping before it was used. "This shows our desire to take the fight against gene doping seriously", says Bengt Saltin, a former member of the WADA committee for health, medicine and research.

Saltin's work into developing tests for gene doping is supported by WADA. "I am convinced that gene therapy will be used in medicine one day without any risks for the patient's health", he adds. "But I think it is unacceptable to misuse this progress to create super athletes. Gold medals should in the future go to those who owe their success to hard work, training and a true love for their sport, and not to some athlete with the best modified genes."

Improving people?

Disrespecting people?

Should gene therapies developed for medical purposes also be used to improve the performances of healthy people?

Almost every medical procedure involves some risk. But we are prepared to accept those risks when it is a question of life or death. Is it responsible though to let otherwise healthy people take the same risks? Especially if gene therapy, and therefore gene doping, are irreversible?

Gene doping is defined as the not medically approved usage of cells, genes and parts of genes, or the modification of the information encoded on the gene, to enhance sporting performances. But what does one mean by medically approved?

Would it be fair to prevent the use of gene therapies by sportspeople if they were widespread in medical care? If patients can see a muscle injury heal much faster thanks to gene therapy, should athletes with a strained muscle also have access to this treatment? Should they be banned from competition? Just where does the boundary between medical and unauthorised usage lie?

There are some who have called for gene therapy to be made available to all athletes. They claim that it doesn't make sense to ban a method that is impossible or at least very difficult to detect. For years those who develop doping methods have always been one step ahead of investigators. And it is also true that for each doping agent, a test has been eventually developed.

Others say that gene therapy will one day become a part of our lives. Why should only plants and domestic animals be genetically improved, they ask? Individuals are committed to improving themselves

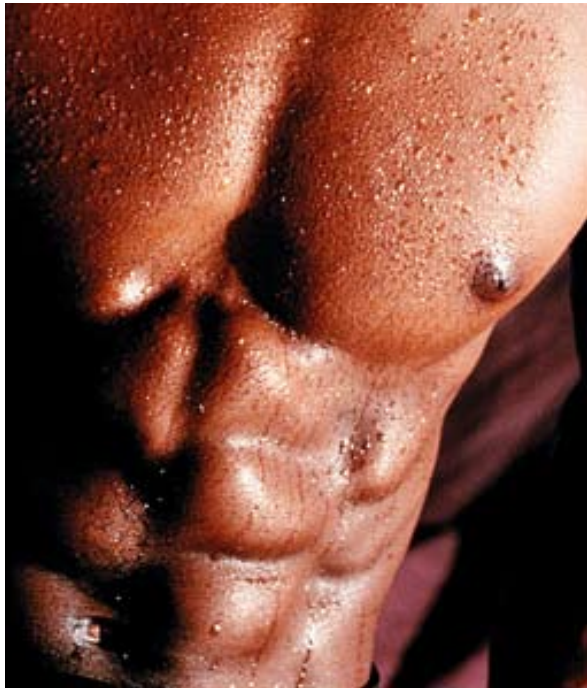
Disrespecting people?

Improving people?

Disrespecting people?

if they have the means. And if we test genetic improvements on individuals, then athletes are the best suited to the task. They are young, healthy, motivated, under regular medical surveillance – and prepared to take risks.

But who will inform these healthy, fit and brave "guinea pigs" of the risks and dangers involved? And finally should everything that can be done be done?



“We are developing a therapy that makes muscles strong”

Professor Nadia Rosenthal, European Molecular Biology Laboratory – EMBL, Monterotondo, Rome

“I hope that someday it will help patients”

Michi Graf suffers from an irreversible muscular disease. Duchenne muscular dystrophy (DMD) means his muscles are slowly wasting away. Today he can still sit in a wheelchair, but one day he won’t be able to breathe on his own. Michi will probably die before his 25th birthday.

Because DMD and certain other degenerative muscular diseases have a genetic origin, researchers around the world are searching for a gene therapy that works. Nadia Rosenthal has mice in her laboratory suffering from a similar kind of muscle wasting, but she has managed to cure them. She transplanted a gene that produces a muscle growth factor known as mIGF-1. This factor protects the muscle and compensates for the gene defect.

The aim now is to apply this therapy to humans and help them build up their muscles again. This research gives hope for patients like Michi Graf.

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