Silicone arteries

*High-tech Polyfilla repairs life-threatening aneurysms*

On 18 April 1955, Albert Einstein succumbed to the results of a ruptured abdominal aneurysm. Earlier, he had refused further treatment: 'I have done my share, it's time to go'. Albert Einstein was 76 years old when he died. The famous French mathematician Jean Fourier and American comedy star Lucille Ball also died as a result of an abdominal aneurysm.

X-ray contrast image showing an aortic aneurysm, i.e. a distended abdominal artery. The cause of the distension is unknown, but possible explanations include smoking, arteriosclerosis, and genetic disposition. The thin white line is the catheter used to inject the contrast liquid.
result of ruptured aneurysms. Aneurysms rank tenth on the list of most likely causes of death. Most non-medical dictionaries offer very little in explanation of the term aneurysm; we have to make do with «vascular swelling». Strictly speaking this is an incorrect description, since the word swelling brings to mind an inflammation, or a tumour. However, an aneurysm is a local expansion of an artery resulting from a weakening of the vascular wall. One 1948 edition of a Dutch encyclopaedia included 830 words and seven illustrations discussing the subject and said that ‘syphilitic inflammation of the arterial wall is the primary cause of aneurysms’. By 1979 the same encyclopaedia devoted no more than 500 words and three illustrations to aneurysm and there was no mention of syphilis. Instead, arteriosclerosis was listed as the primary cause.

During the latter years of his life, Einstein suffered regular attacks of pain in the upper abdominal region, caused by gallstones. A grapefruit-sized swelling of the aorta was detected by coincidence (as is the case in most instances today). Surgical examination revealed this to be an aortic aneurysm. The aneurysm was found to be intact, with a firm vascular wall, so it was decided not to proceed with further treatment. Suffering from an aortic aneurysm is like carrying a ticking time-bomb around, knowing that the main artery in your body may collapse at any moment, offering little hope of survival. More than six years after the diagnosis was made, the aneurysm ruptured, and Albert Einstein died. The following day the New York Times described the cause of death as 'a big blister on the aorta, which broke finally like a worn-out inner tube.'

Wear and tear

Dr. Alexander de Vries works as a vascular surgeon at the Haaglanden Medical Centre, The Hague. Together with Dr. Hans Brom, vascular surgeon at the Kennemer Gasthuis hospital, Haarlem, he has developed a new method of repairing aneurysms. The current method of treatment always involves major surgery. ‘The main body artery, the aorta, starts at the heart, curves down in the chest cavity, and continues downward to roughly the level of the navel,’ De Vries explains, ‘where it divides into the two arteries that continue down into the legs. Just above the division is the place where most aneurysms occur. Normally, the aorta measures about two centimetres in diameter, but an aneurysm may widen this to five centimetres and more. It is a form of wear and tear, the exact cause of which is still unknown. We also don’t know why it tends to occur just above the bifurcation. An aneurysm usually occurs without the patient knowing anything about it. There are no symptoms, until the aneurysm ruptures. When that happens, and if you make it to the hospital and into the operating theatre in time, your chances of survival are only about 50%. So in fact, aneurysms are mostly detected by chance. People come in for an abdominal examination, for example because they have a kidney complaint, or something wrong with their gallbladder, and the aneurysm is stumbled upon in the process. In very rare
cases, patients may complain that it feels as if their heart is pumping in their belly, in which case it usually is a very large aneurysm, which can be felt by placing your hand over it. But these are extreme cases. There is some talk about screening the population, for slight aortic dilations occur in roughly ten percent of all males over the age of 65. Currently, we have two surgical procedures for treating aneurysms, but these operations carry a high health risk, not so much because of the aneurysm itself, but rather because the operations can have a severe impact on patients, even on otherwise healthy people. The surgeon gains access to the abdominal aorta through the femoral artery in the groin. The abdominal aorta has to be temporarily clamped. The chances of surviving the operation are about ninety-five percent, in other words, one in twenty patients dies as a result of the operation.

Aneurysms mainly occur in people over the age of 65, and in men more often than in women. The cause is unknown, but it may have something to do with the fact that men currently «outdistance» women regarding smoking-related diseases. About a century ago, the Amsterdam surgeon W.M. de Vries (not related) conducted a statistical survey into aneurysm incidence. In a total of 7500 post-mortems, he found 181 large aneurysms, 120 were in the aorta (99 males, 21 females).

Bifurcation prosthesis
The traditional method of treatment involves replacing the section of the aorta in which the aneurysm is located with a synthetic blood vessel.
De Vries: 'De aorta is clamped above the aneurysm, as are the two branches feeding the legs. The section of aorta between the clamps is replaced with a bifurcated prosthesis, which looks a bit like a pair of trousers.' Most of these artificial arteries are made of polyethylene terephthalate (better known as pet). They are knitted or woven using threads only 10 micrometres thick. In the alternative method, the abdominal wall is not penetrated, and instead the surgeon gains access to the abdominal cavity through the groin. This is known as the endovascular method, in which the surgeon inserts a prosthesis into the aorta via both groins. There it is secured by metal springs.
De Vries: 'These so-called graft stents are rather big, so the procedure still requires quite a surgical access to the arteries. And even though this type of treatment puts much less stress on the patient, there is no proof yet that it works as well as the traditional method.'
The trend in modern surgery is to reduce the need for large incisions, and to perform operations through small incisions instead.
'De Vries says. The newly developed method for treating aneurysms will no longer involve any incisions at all, as it requires only small punctures. De Vries: 'Our plan is to inflate a small balloon inside

(A) Conventional surgical method to replace the aneurysm with a bifurcated prosthesis through an incision in the abdominal wall.
the distended aorta which will both temporarily block the flow of blood and form the mould in which we can allow a filler to cure. In this way we can cast a new interior wall for the artery, filling the aneurysm cavity in the process. When that is done the balloon is removed, and hey presto!’

However, all is not over yet for Dr. Alexander de Vries, for one crucial question remains, and that is what type of material to use for this method. Medical supply companies don’t list fast-curing, flexible, biocompatible Polyfilla in their catalogues.

De Vries: ‘The basic idea for treating this medical condition had been elaborated, and it required a specific material with several essential properties. Queries to a number of supply companies yielded no results. I was pretty certain that the material was not something you could simply order from stock, and that it had to be made especially for us. And then I saw an article in the paper about «solid water», which was something invented by Prof. Jan van Turnhout at the tu delft. By adding a small quantity of a special polymer, he was able to increase the viscosity of water at will. This might well be the material I was looking for, so I decided to see Van Turnhout about it.’

Biocompatible
Professor Jan van Turnhout works at the Polymer Materials & Engineering Section of the Department of Chemical Engineering. Together with researchers Ir. Larbi Alili and Otto van den Berg M.Sc. he has spent the last eighteen months developing a material that can be used for the method developed by De Vries.

Van Turnhout: ‘The funny thing is that De Vries found us through the «solid water» article, for the polymer discussed in the article is totally unsuitable for his application. Even so, it serves to illustrate the immense diversity of polymers. With the ever-increasing number of available syntheses and fillers (such as nanoparticles) it has in fact become possible to make polymers to measure. The requirements De Vries proposed for his material are highly specific, and before he came to us, he had become convinced that it could not be bought off the shelf. So of course, it became a real challenge to develop such a material.’

The requirements are very strict because the material is to be implanted in the human body, the requirements are very strict. The material may not contain any soluble components, and it may not be degraded by the body. In addition, it has to be biocompatible, i.e. it may not cause any changes in the surrounding tissue, or allergic, carcinogenic or toxic reactions, it may not interact with the immune system, and may not cause thrombosis. And of course it has to be sterile. On top of this medical wish list comes the need for the material to have good flow properties in the liquid stage and good mechanical properties when cured. Since the material is introduced into the body through a thin catheter, its flow resistance (i.e. its viscosity) had to be low. The internal diameter of the catheter used for the purpose is only about one millimetre, and even at a low viscosity, a pressure of about 80 bar is needed to squeeze the material through. The material has to cure quickly (in less than five

(B) An alternative method uses an endoprosthesis, a synthetic sleeve that is fixed to the inside of the aorta by means of metal braces called stents. The sleeve is surgically inserted via the arteries through the groins.

Metal stent, which is expanded (using a balloon catheter) to fit against the inside of a blood vessel in order to locally reinforce the blood vessel wall, or to hold a synthetic sleeve in place.
minutes), for during all that time the flow of blood through the aorta is blocked by the balloons, so the legs, and even more importantly, the kidneys, are deprived of oxygen. Once cured, the material's mechanical properties also have to pass muster. If we take a conservative estimate that the treatment will extend a patient's life expectancy by 10 years, a simple sum tells us that the material must be able to withstand over 400 million pulses.

Mega molecules
Polymers consist of long chains of identical molecule groups. For example, polyethene (the soft plastic used to make most of today's shampoo and detergent bottles) consists of a long chain of carbon atoms attached to hydrogen atoms on either side. Leaving aside the material properties of polyethylene and similar polymers, their production method precludes their application in endovascular injection moulding. Having examined a large number of polymers, the Delft researchers soon got to polyurethanes and silicones. Polymethyl siloxane (pDMS), also known as silicone, is the most obvious choice for this application as it has been in use for human implants for over 30 years. Its polymer chain contains silicon and oxygen atoms, and the lateral groups attached to it determine its specific properties. In many ways, polysiloxanes are a special material, highly diverse, and with a wide application range. In its liquid form it is easy to process and after curing it is flexible and tough with good adhesive properties. This makes it ideal for making transparent structures, such as a waterproofing sealant, e.g. fully transparent fish tanks. Plastic surgery is not the only field in which it is a favourite material for use in implants, make-up artists also like to use it. In Little Big Man, for example, a silicone mask was used to transform Dustin Hoffman into a 121-year old Indian chief. Silicones are increasingly being used to manufacture spare parts for the human body. In addition to breast implants, heart valves, and contact lenses, the material is also being developed for use in finger, toe, and wrist joints, penile inserts, artificial skin, artificial hearts and lungs. There was even a contraceptive device, the oviductal plug, in which a silicone plug served to block the ovaries. It has been abandoned. Silicone is highly permeable to oxygen, making it eminently suitable for the manufacture of contact lenses. To demonstrate this property, a number of snails were once completely embedded in silicone. The creatures survived the experiment which was not conducted at the tu delft, by the way for 72 hours. Unfortunately, breast implants have badly tarnished the reputation of silicone as a material for medical applications. Undeservedly, according to Van Turnhout: 'Use the word «silicone» in the same sentence as «medical application», and you will find yourself shut out. This is of course the result of the problems that occurred with breast implants. Curious, in fact, since it most certainly wasn't the silicone that caused the trouble, but rather the oil used to fill the implants. Silicones are completely inert, but if the oil is released, it might cause health
problems. The effect of the whole episode has been to have silicone rejected for medical applications.' Which is why getting hold of the stuff requires a few white lies from time to time. The most recent subterfuge is to order it 'for an aerospace application'.

Nanoparticles
To minimize the curing time, Otto van den Berg experimented with various catalysts. The special requirements for a catalyst are that the quantity needed should preferably be very small, and that it must be an inert material that does not affect the human body, nor the properties of the polymer. Van den Berg discovered the ideal catalyst in the form of a precious metal that fits the bill perfectly: it is completely inert, and only a few parts per million are required to ensure that the polymer cures within five minutes. However, the first experiments with the silicone polymer were not a success.

Van Turnhout: 'Although it cured fast enough, and the viscosity was all right, the mechanical properties were not up to scratch. If you pulled it, it tore apart. It simply wasn't strong enough. We solved the problem by adding a filler to reinforce the polymer. In most cases, the best results are obtained when the filler is closely related to the material. We are now using very fine, round silica nanoparticles measuring only a few nanometres across. An additional benefit of using silica is that it shows in x-ray photographs. Unfortunately, these particles are known thickeners, so they increase the viscosity. On the bright side, we managed to find nanoparticles that do reinforce the material, without increasing the viscosity. New developments in this field come in such rapid succession these days, and we're only just starting to see the potential applications.'

As an example Van Turnhout describes a nanoparticle with special groups ('arms') that will further improve the adhesion to the polymer. And glass fibres with a diameter of only 0.2 micrometre, i.e. one five-thousandth of a millimetre, are now available. The diameter of a human hair is about 100 micrometres, or 500 times that of the glass fibre. In a catalogue the size of a telephone directory, Alili has marked a couple of chemicals to be tested as candidates for further improving the silicone polymers. For each of the materials listed, the catalogue includes the structural formula, the viscosity, the specific mass, and of course, the price. The latter is of some importance, since compounds can differ in cost by a factor of one hundred.

Good mix
A work top in the laboratory is covered in test pieces of different materials. Some look just like one would expect, i.e. like bits of cured silicone sealant. Other pieces are almost completely transparent. This is caused by the addition of the silicate nanoparticles. The nanoparticles are smaller than the wavelengths of visible light, and as a result the waves of light fail to notice the particles, passing them by and showing the material as transparent. On their own, the two components that will form the polymer are not reactive, but if one component (silicone and silicate particles) is

Example of the chemical structure of a silicone polymer (polydimethyl siloxane). Derivatives of this polymer are used for the aneurysm project.

SEM image showing the surface of a fracture in a silica-reinforced silicone polymer.

The ingredients for the arterial lining in an aneurysm cavity consist of: Base polymer (centre) and silica nano-powder particles (on the right). The mixed preparation is in the background, and on the left is a model for mechanical lifetime testing.
mixed with the other (silicate particles plus catalyst), it starts a reaction that in five minutes produces the flexible and strong material. The important thing is to mix the two components quickly, but most of all, thoroughly. Van Turnhout found the solution to this practical problem on the Internet. It is a device that looks like a syringe with two compartments that are joined in a long tube. Inside the tube, the two flows are forced through the helical path of a static mixer to obtain the best possible mix.

Ethics
In the cellar, Gerard de Vos, the group's technician, has set up a number of mechanical wear experiments. There is a machine that inflates and deflates a silicone polymer tube three times per second. In the corner is a tensile strength tester that has been stretching a piece of material to 1.6 times its length for the past three months, 24 hours a day, 1260 times per minute. These tests stress the material to a point far above the limits likely to occur inside the human body. The aorta for instance, stretches only a fraction of a percent. Even so, the material passes every test with flying colours. Once the material has reached its final composition, the next phase commences. First, the right types of catheters will have to be developed to insert the balloon and the silicone mix. One option is to use a modified version of the catheters used for angioplasty, in which heart patients with coronary stenosis are treated by inserting a balloon into the artery in the groin and moving it up to the coronary artery. Once there, the balloon is inflated to stretch the constricted part. Models will have to be made to test the method with the various known types of aneurysms, which come in all shapes and sizes. For very complex shapes, a number of balloons may be used together to form the mould. This will very probably be followed by animal experiments, after which the method can be applied to humans. The question then is who will make the most suitable human guinea pig. Should it be a patient who has been given up by the medical profession, or should we use a relatively healthy person? De Vries: 'This is a very complex problem of ethics, but in real life it will probably turn out to be someone who cannot be treated in any other way, there won't even be a choice. The first time is always a bit of an experiment.'

From surgery to procedure
What makes the method developed by De Vries and Brom (and elaborated by trainee surgeon John Vlot of the Haaglanden Medical Centre) special is the fact that it is no longer a major operation. It now qualifies as a «procedure», in which needles and catheters take the place of scalpels. The traditional work of the surgeon has been replaced by a few arterial punctures through which catheters can be inserted to deposit their materials at the location of the aneurysm. Using x-ray imaging, the physician will conduct the high-precision procedure by remote control. There is something else that makes this method unique.
De Vries: 'The remarkable fact is that we will soon be building something inside the body. This is a first, for until now everything that we put into a person is
constructed outside the body before it goes in. But this is a custom job, and that opens a whole new range of options. It might be used for fractures, urological applications, plastic surgery, and so on.’
Van Turnhout is also enthusiastic: ‘The crucial fact is that the basic ingredients have now been developed, so hospitals can actually start to think about using them one day. To us, this project was a real eye-opener, since neither universities nor the industry are putting much effort into research on the medical applications of polymers, even though it is a subject of enormous social impact. Added to which it is of course good business. Take an angioplasty catheter for instance. Its added value pushes up the price to several hundreds of euros, while the amount of material it contains hardly costs anything.’

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The aneurysm can be reached from up to three puncture locations using guide rails along which the catheters can be positioned in place.

Example of an aneurysm being treated by means of three balloon catheters. The tip indicated by the arrow is an echo sounder used to determine the location of the renal arteries.
Each type of aneurysm has a specific shape for which the correct shape of balloon catheters must be used.
Silicones are also used by make-up artists. The pictures show actress Carrie-Anne Mos being transformed into an old man.