Can we fix ‘spelling errors’ in genes?
CAN genetic diseases be cured? An example of a genetic disease is the condition porphyria variegate, found in some South Africans, which geneticists tracked back to the arrival of a Hollander, Gerrit Jansz, and his wife Ariaantje in 1688. They had many children and passed on the gene (responsible for porphyria). It gives a blistering skin rash in the sun, which isn’t a problem if you stay in the shade.

But it became a problem in the early 20th century when people (with this gene) being given barbiturate anaesthetics were dying abruptly because of their incapacity to metabolise that drug. In a sense here is a genetic disease that, once identified, could be treated provided the person stayed out of the sun and didn’t take barbiturate anaesthetics. But that doesn’t mean it’s cured, because the person’s still carrying the spelling mistake in that gene.

But we do treat and cure many people with genetic diseases. A colleague in Virginia, USA, saw the case of a boy who had mousey brown hair, was autistic, and unable to speak. He immediately recognised the symptoms of phenylketonuria and put the boy on a phenylalanine-free diet, meaning its levels in the bloodstream changed. He was given tyrosine, an amino acid key to melanin pigment which the boy’s body couldn’t make, and his hair went black. Sadly he didn’t learn to speak because the phenylalanine in his blood had destroyed parts of his brain irreversibly.

Today we have Guthrie cards (which use blood spot testing) to screen for this rare condition so that we can put children on a phenylalanine-free diet. This is a genetic disease we treat by adjusting the diet.

Another common gene which many people in South Africa carry causes sickle cell disease. For people who are derived from ethnic groups in the African Rift Valley or malaria zones, one in three have it. It’s a good gene, in that you rarely die of cerebral malaria. Unfortunately if you inherit it from both parents, then your haemoglobin sticks together, producing sickle shaped blood cells. These break down, causing you to mass-produce blood so that parts of the body, like the skull, become swollen trying to keep up with the loss of blood cells.

We can treat this by transfusion but we can’t cure it because we can’t extract that genetic spelling mistake from the population. We can identify when both (in a couple) carry sickle cell disease, and they might choose not to have children, or they might choose prenatal diagnosis.

So many diseases like this are not obviously curable but we are start-
NEW FRONTIERS: A microscopic view of a colony of human embryonic stem cells growing on fibroblasts. The writer says stem cells could repair genes responsible for genetic diseases.
New genetic sequencing technology extends our capacity to identify genetic disease, but it still doesn’t cure disease.

Genetic sequencing has exploded in the last decade. The Human Genome Project was an international effort enabling us to identify the whole sequence of the human genome. Two years ago geneticists at Leiden University, using new generation sequencing, sequenced one of their genomes in their spare time in a laboratory for €45,000 (R419,000).

With the latest technology in sequencing we were able to sequence a new bacterium in 12 hours. Had we done that in 1990 using older techniques, it would have taken two people, working flat out, 100 years to complete.

Stellenbosch University is developing a handheld sequencer that uses nano wires and can identify who carries particular disorders in minutes. It can also identify HIV while you wait, by sequencing the genome.

New sequencing technology extends our capacity to identify genetic disease, but it still doesn’t cure the disease.

A woman, Alison, 50, came to see me two years ago because she had lost many members of her family to breast cancer, including her mother and grandmother. I took a sample and sent it for sequencing of the BRCA1 and BRCA2 genes (responsible for genetic breast cancer).

Alison couldn’t get referred to our clinic despite the fact that she had had a breast cancer at 34. While I was waiting for her results, she turned up at her local hospital unable to speak, having had a stroke. An ultrasound of her pelvis found ovarian cancer which had metastasised to her brain, causing the stroke. She had treatment but just as we discovered that she did have the spelling mistake in her BRCA1, the tumour recurred and she died.

This wouldn’t have happen if we had high speed sequencing. Had I found that BRCA1 mutation a year earlier, we would have referred Alison to have her ovaries removed because it’s been shown that women with these mutations, who have their ovaries removed, have a much lower incidence of ovarian cancer.

The medical chemists and oncology teams at Newcastle are looking for drugs to treat cancer. They discovered an enzyme involved in repairing DNA. If a strand of your DNA snaps, which happens all the time, these enzymes repair it. Cancer is rapidly dividing and therefore more susceptible to DNA repair damage. The idea was to look for chemicals that will upset this DNA repair process, repair “inhibitors”.

One such drug was found that could work effectively on people who carry mutations in BRCA1 or 2 genes. The drug is not on the street yet, but this was producing a huge response in people with hereditary breast and ovarian cancer.

It’s not a magic bullet but it’s very effective in these patients. We’ve got the first example of a cure for a genetic disease. The problem is identifying the people who have that genetic disease, using faster sequencing. I predict that in the very near future, if you presented with breast cancer at a young age, you would want to know if you have the BRCA1 or BRCA2 in order that you can get access to these drugs.

Another approach to dealing with genetic disease is simply to replace and repair the bits in the genes that are broken. This doesn’t just apply to rare genetic diseases, it applies to more common genetic diseases like insulin dependent diabetes.
Stem cells opened up this opportunity a decade ago. We started working with embryos because the cells in the early embryo are undifferentiated, meaning they haven’t been told what to do yet. And if you keep those cells in culture, as primitive cells, they are capable of doing anything. The hope is to be able to manipulate them so that they could turn into any tissue that you wanted them to. A colleague of mine can now cause embryonic cells to turn into blood cells, meaning instead of people with sickle cell disease having transfusions, maybe we can give them new and improved marrow.

We’ve shown that if you leave embryonic stem cells long enough, some of them change into cardiomycocytes, cells that make up the heart muscle, and start beating in the dish. If we could control that process, then for someone who has a damaged myocardium or has a genetic disease like cardiomyopathy, we might be able to generate cells to repair that lost tissue.

The ability to harvest and manipulate adult stem cells is very exciting. A member of our team has worked out how it might be possible to take the neural crest cells in hair from the back of your neck and convert those into primitive nerve cells in order to restore a severed spine. It’s been done successfully in rats.

My final story is about a patient, Jonathan, who has a genetic disease called familial adenomatous polyposis (FAP) caused by a spelling mistake in a gene that controls the division of stem cells in the gut. Thus the stem cells grew out of control and form polyps. In any colon cancer, the first gene that goes wrong is the associated gene, the familial adenomatous polyposis gene. It is the guardian of the cells in your gut. So to get at the cancer you need to take that one out first. It struck me that if we could find a way of treating someone like Jonathan that would slow down his disease it might be good for the whole population.

Several years of research in different populations around the world, including here in Namaqualand, showed that taking 600mg of aspirin daily for two years, drastically reduces the chance of getting colon cancer. The University of Cape Town’s Division of Human Genetics was instrumental in this research. So we now have a treatment for hereditary colon cancer. The next step is to see whether lower doses of aspirin have the same effect.

Professor Burn is the head of the Institute of Human Genetics at the University of Newcastle in the United Kingdom. This is an edited version of his lecture “Can we cure Genetic Disease?” as part of the 2010 Darwin Seminars hosted by the African Genome Education Institute.