

TOO MUCH OF A GOOD THING

WE NEED IRON, BUT EXCEEDING NORMAL LEVELS CAN LEAD TO SEVERE ORGAN DAMAGE. MODERN TESTS ALLOW THE PROBLEM TO BE PICKED UP AND DEALT WITH LONG BEFORE IT COMES TO THAT, WRITES PETER LAVELLE.

PHOTOGRAPHER: MARINA NEIL

Two decades ago haemochromatosis, an iron overload disorder, was thought of as rare. In fact, it is one of the more common genetic disorders, something we now know thanks to genetic tests that have made diagnosis much simpler.

Accurate and early diagnosis is important, because it is a chronic illness that over the longer term can cause cirrhosis of the liver, diabetes, arthritis and heart disease if not treated.

The problem is one of iron metabolism. *Haem* means blood and *chroma* refers to the bronze colouring of the skin someone in the advanced stage of the disorder may get.

Iron metabolism

Our bodies need iron – it's a vital component of haemoglobin, a protein found inside red blood cells that is responsible for transporting oxygen to body tissues. Most of the iron comes from our diet.

In haemochromatosis, for reasons not fully understood, the body absorbs more iron than is needed. We typically store about one gram or less at any given time. A person with haemochromatosis can store five grams or more.

This additional iron ends up in the tissues of organs such as the liver, heart

and pancreas. Without treatment, haemochromatosis can cause these organs to fail, leading to death.

The condition hits men and women equally, but usually shows up later in life in women, who tend to lose more iron than men earlier on as a result of menstruation. It takes time to build up and cause damage, so the problem usually doesn't manifest until a man is in his 30s or 40s and later for women.

Haemochromatosis is largely limited to people of North European extraction, says Dr Peter Hickman, a chemical pathologist at the Canberra Hospital and the

Today, with more pathology tests being conducted, it is almost always picked up during analysis of a blood test done for some other reason. Hence it is far less common these days for patients to present with the symptoms undiagnosed, says Dr Hickman. “In practice, it’s almost always diagnosed well before symptoms develop,” he says. A significant victory for modern pathology.

Australian National University. It is rare in Asian populations, he says.

The list of symptoms is long, and the liver, which accumulates more iron than other organs, can be particularly hard hit. Reproductive organs and joints can also be affected.

The condition can cause weakness, lethargy, chronic fatigue, abdominal pain, arthritis, loss of sex drive, impotence in men, absent or scanty periods and early menopause in women, a decrease in body hair, discolouration or bronzing of the skin, disease of the heart muscle, impaired memory, mood swings, severe irritability, and depression.

Many other conditions have these symptoms, and it used to be that haemochromatosis was not diagnosed until it was in its advanced stages. Because doctors often failed to make a diagnosis, it was considered a rare problem.

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In the genes

So what’s behind haemochromatosis? We now know that it is caused by a genetic mutation known as C282Y, on chromosome 6, which was first identified in 1996. (There are some other mutations that have been linked to haemochromatosis, such as S65C and H63D, but their significance is debated.)

Some people believe that a combination of a C282Y and an H63D

mutation is associated with iron overload, but Dr Hickman doesn’t buy this. “In fact these mutations are no more or less prevalent in people with haemochromatosis than in the general population”, he says.

The C282Y mutation, for reasons not fully understood, leads to the production in the liver and other organs of free radicals that damage cell membranes, Dr Hickman says. If the condition is not treated, the damage may lead to fibrosis, which may progress to the advanced stage known as cirrhosis and finally liver failure.

Dr Hickman believes this mutation has survived in the human gene pool because of the widespread prevalence of iron deficiency in some North European populations. The mutation may have given people with it an evolutionary advantage, allowing them to absorb more iron.

He says there is an especially high incidence of C282Y in Ireland, a country that experienced repeated famines and one where people would have had diets low in iron.

About one in 10 people of North European background are carriers – that is, they have one C282Y mutation. Carriers won’t develop the condition themselves, but may pass the mutation on to their children.

If two carriers conceive, their child has a 50 per cent chance of inheriting one C282Y gene and becoming a carrier, and a one in four chance of inheriting both C282Ys.

Between one in 300 and one in 400 people will have two C282Y mutations, meaning they are at risk of haemochromatosis but might not end up with the condition.

Only about one-third of cases will go on to have the clinical picture of haemochromatosis. Another third will

never get the full condition but will have raised iron levels, and the remainder will have normal iron levels, Dr Hickman says.

Carriers may have raised iron levels but almost never get haemochromatosis. They don’t get liver disease, for example, unless they have significant alcohol consumption.

The diagnosis

Twenty years ago, it was normal for the condition to be diagnosed with the aid of a liver biopsy. A needle was inserted into the liver under local anaesthetic to remove a sample of liver tissue that was examined for iron content.

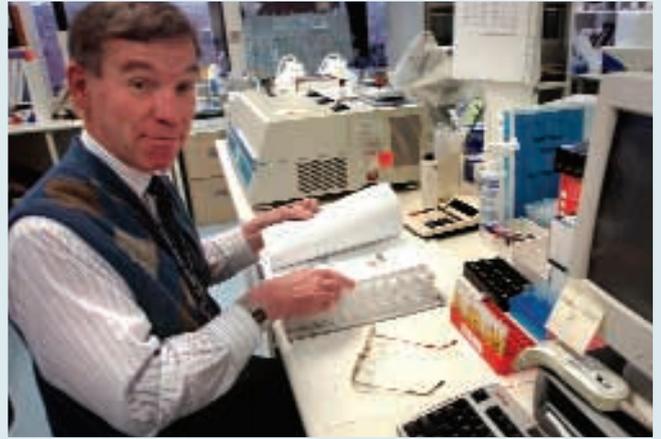
This entailed a small degree of risk, mainly the possibility of bleeding after the inadvertent puncture of a blood vessel in the liver. However, liver biopsies are less common these days. Instead, iron studies and genetic testing are used to make the diagnosis.

Iron studies involve looking at the compounds involved in iron transport and storage in the body as well as levels of iron in the blood. Levels in the blood fluctuate, so on their own they will not reveal a person’s true iron status.

In the body, iron is attached to special transport and storage proteins. The transport protein is called transferrin. So pathologists measure the percentage of iron bound to transferrin. They also measure ferritin, which is the protein used to store iron in the tissues.

These measurements combined give a good idea of the total amount of iron in the body. Two blood samples on different occasions are needed to confirm raised iron levels, because serum ferritin can fluctuate in certain conditions, such as after a high alcohol intake.

While the diagnostic tests are high-tech, the same can't be said for the treatment. Bleeding is a practice that was used by doctors in antiquity for many ailments. It was thought to release bile, phlegm and other so-called humours that were believed to cause illness.



Dr Peter Hickman, a chemical pathologist at the Canberra Hospital and the Australian National University.

If the figures are raised after two samples, then genetic testing is the next step. Such testing was first introduced in 1996, shortly after the C282Y mutation was discovered.

Many genetic laboratories offer tests for the C282Y mutation which will detect people with one or with two of the mutated genes.

To treat or not to treat

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And it survives today as the treatment of choice for haemochromatosis, although doctors tend not to use the term "bleeding" because it conjures up images of leeches and medieval mortuaries. Instead the treatment is called venesection, or phlebotomy. It involves the patient regularly giving blood – 500 ml usually at a sitting.

Once the blood is removed, the bone marrow makes more blood cells to replace those lost, and in doing so uses up the excess iron stores. Stored iron and ferritin levels gradually fall, limiting the organ damage that would otherwise have occurred over time. As with donating blood to a blood bank, the procedure is safe.

How often does it need to be done?

That's a question about which there is much debate among pathologists (both haematologists and chemical pathologists) and gastroenterologists.

All agree that people with haemochromatosis need to be treated, as do people with very high levels of

ferritin and transferrin who are likely to go on to get the disease. The general consensus is that they need to have venesection weekly or even twice weekly, until ferritin and transferrin saturation levels come back to normal. This may take up to 18 months. After that, blood needs to be taken three or four times a year for the rest of the patient's life.

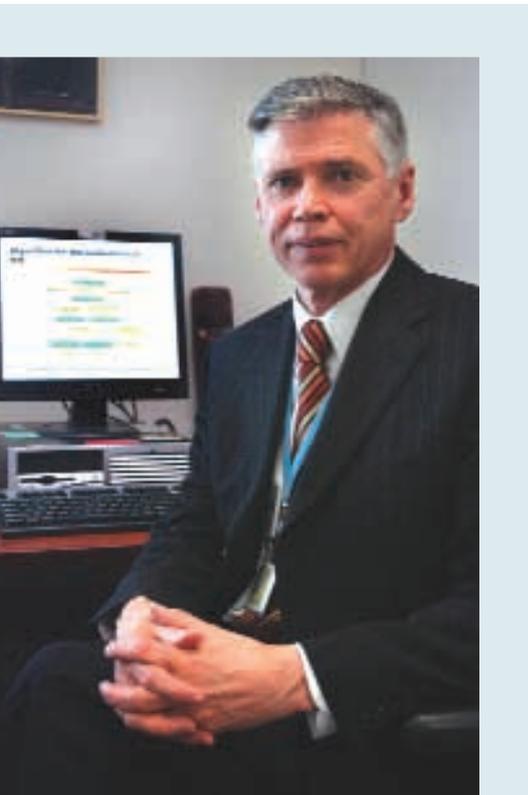
But what about people who have the mutation, but only mild abnormal iron studies – do they need to be treated? Dr Mark Bassett, a gastroenterologist at the Canberra Hospital, believes it is sensible to treat all cases of iron overload.

"We don't really know at what level people get symptoms from iron overload; it's probably at a serum ferritin of around 500 ug/L (micrograms per litre), but it does vary," he says. (The normal range is 20 to 300 ug/L for males and 10 to 200 ug/L for females.)

So, over 500ug/L, they should be treated aggressively, with weekly venesection until the ferritin comes down below 100ug/L, he argues.

And at ferritin levels below this, say in the range of 300 to 500 ug/L? Treat them but less aggressively, he says. For instance, venesection every two weeks, until the ferritin comes down below 100 ug/L. Both groups should continue life-long venesection, usually three to four times a year. 🔥

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>



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