Irish Haemochromatosis Association

Iron Overload

HANDBOOK

2016

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This handbook is not a substitute for medical advice. Anybody who is concerned that they might be affected by haemochromatosis should consult a doctor.

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Note

The clinical advice in this edition is based on the EASL Clinical Practice Guidelines for HFE Haemochromatosis published by the European Association for the Study of the Liver which are online at http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-hfe-hemochromatosis

Table of Contents

INTRODUCTION

Haemochromatosis is an inherited condition in which an excess of iron is absorbed from the diet and stored in the body. The excess iron can in turn give rise to a range of medical problems.

The body can become overloaded with iron for other reasons, including repeated blood transfusions and (rarely) excessive consumption of iron supplements. These non-inherited causes of iron overload, sometimes referred to as “secondary” or “acquired” haemochromatosis, are not covered here. In this handbook haemochromatosis always means inherited (genetic) haemochromatosis and except where indicated means Type 1 haemochromatosis.

About 1 in 83 Irish people are at risk of developing haemochromatosis. About 1 in 5 people are carriers of the altered gene that can cause it.

In 1996 it was discovered that a mutation of one gene, known as the HFE gene, greatly increases the risk of a person and, perhaps, their blood relatives developing haemochromatosis. People with two copies of the gene mutation have a significantly raised probability of accumulating life threatening levels of iron stored in their body. It is easy to test whether someone has inherited the mutation. This provides an excellent opportunity to identify and diagnose those people most at risk of suffering permanent organ damage long before it occurs.

Nevertheless, many sufferers are only identified after major organ damage has occurred. Haemochromatosis is neither

well known nor routinely suspected by the public at large or by many members of the medical profession. The test for raised iron is not often ordered by doctors.

With early diagnosis and effective management of the disorder, potential sufferers can live normal lives free from the risk of the life threatening effect of haemochromatosis. Treatment requires neither drugs nor surgery.

Aims of the Handbook

The aims of this handbook are to:

- improve awareness and knowledge of haemochromatosis;
- provide information to all interested persons about the nature of this disorder;
- assist in the early identification and treatment of those most at risk, to avoid the life threatening consequences of uncontrolled iron overload;
- assist carriers, sufferers and other interested persons with an understanding of the diagnosis and management of this very common genetic disorder.

1. HAEMOCHROMATOSIS

Haemochromatosis is an inherited disorder which causes the body to absorb too much iron from the diet. The excess iron gradually accumulates, usually in the liver, pancreas, joints, heart or endocrine glands. Simple and effective treatment is available, but if the excess iron is not removed irreversible damage can eventually occur, especially in the liver.

1.1 What is Haemochromatosis?

Haemochromatosis is the condition of iron overload in the body. The iron overload comes about because the body continually absorbs more iron from the diet than it needs. The body is then unable to rid itself of the excess. The excess slowly builds up over a number of years and damages the organs where it is stored. It is rare for iron to build up to a damaging level in childhood, and it often does not happen for several decades.

The underlying cause is the inheritance of a mutated gene. The faulty gene stops the normal body iron control working properly. A faulty gene, and therefore haemochromatosis, can only be inherited. Haemochromatosis cannot be caught from somebody else, nor can you give it to someone else, except by having a child. Haemochromatosis is a recessive disorder; this means that it only develops if you receive two copies of the mutated gene, one from each parent.

Although haemochromatosis is closely associated with one particular gene mutation, not everybody who has inherited that gene mutation will develop iron overload; indeed the proportion that does so may be quite small. Inheritance of the mutated gene greatly increases the *likelihood* of developing haemochromatosis but does not on its own cause haemochromatosis; other factors must be involved, but it is not yet known what they are.

A normal man has about 4 grams (g) of iron in his body, mostly found in haemoglobin in the red cells of the blood. Up to 1g is stored in the tissues and may be used to make new haemoglobin if required. With haemochromatosis it is this amount stored in the tissues, the “storage iron”, which becomes excessive. A woman has 3-4g of iron, of which the storage iron is usually less than 0.5g. Overload is said to occur in individuals when their stored iron rises to 5g or more; it may rise to 40g.

1.2 The Inheritance of Haemochromatosis

A gene called the HFE gene is involved in the regulation of iron absorption. (HFE is simply the name of the gene - what it originally stood for is not certain). Mutations of this gene are closely connected with haemochromatosis. The main mutation is known as C282Y. About 1 in every 200 people have the C282Y mutation in both copies of their HFE gene. More details about genes and how mutations are passed from parents to their children are given in Chapter 3.

About 90% of haemochromatosis sufferers have the C282Y mutation in both copies of their HFE gene; it is much the most common cause of the disorder, and is also known as Type 1 haemochromatosis. Sometimes another mutation called H63D is inherited with C282Y and may cause iron overload. About 4%

of sufferers have one C282Y HFE gene and one H63D HFE gene. There is another mutation called S65C but this does not on its own cause iron overload.

People with a mutation on one copy of the gene and one normal gene are referred to by doctors as heterozygotes and are carriers; people with the same mutation of both genes are called homozygotes; people with the C282Y mutation of one gene and the H63D mutation of the other gene are called compound heterozygotes.

There are also some cases of haemochromatosis associated with changes in other genes; those coding for hemojuvelin (Type 2a), hepcidin (Type 2b), transferrin receptor 2 (Type 3) and ferroportin (Type 4). However, these are rare and in total account for under 5% of cases of genetic haemochromatosis.

There are recorded cases of inherited haemochromatosis where the abnormal gene has not been identified yet.

1.3 How Common is Haemochromatosis?

Although the very large majority of people whose bodies overload with iron are either C282Y homozygotes or C282Y/H63D heterozygotes, only a minority of the people who have these mutations will develop iron overload and therefore have haemochromatosis. Some further factors seem to determine whether they will actually overload. What these factors may be has not
yet been discovered. It is not yet clear what proportion will overload. Some studies suggest that it is a very small fraction.

While compound heterozygotes have a significant risk of iron overload, its severity is milder than for homozygotes for C282Y,

and few develop major complications. Individuals rarely iron overload if they have only one gene which has either the C282Y mutation or the H63D mutation, or if both of their genes have the H63D mutation. There are usually other factors involved if they do.

Women may overload to a lesser extent than men as physiological blood loss (menstruation and pregnancy) can help reduce iron build up in some instances. Blood donation may delay the build up of iron overload in both men and women.

2. IRON OVERLOAD

In the early stages of haemochromatosis there may be no evident signs or symptoms. It usually takes many years for significant iron overload to occur, and it takes even more for organ and tissue damage to become evident. If signs and symptoms are present, they could take any one of many forms. Even in fairly advanced cases the patient may not display clear, tell tale symptoms. This is why haemochromatosis is often under-diagnosed. Persistent lethargy and tiredness are the most common complaints.

Diagnosis at an early age leads to less or no organ damage. On the other hand, the older the individual at the time of diagnosis, the higher the iron storage levels and the greater the amount of organ damage. The most common age of diagnosis for members of the Haemochromatosis Society was 52, but the range was from 26 to 77. People are being diagnosed earlier today because of the increased awareness of the condition.

2.1 Iron Overload and Organ Damage

Organ damage is one of the most serious complications of iron overload that can occur in the undiagnosed patient. The organs that are most often affected are liver, heart, pancreas and other endocrine glands.

There is little evidence that very minor degrees of iron overload in individuals who are heterozygous for C282Y, H63D or S65C are associated with organ damage.

2.2 Major Complications

Major complications that sometimes arise from haemochromatosis include:

Liver disorders

Fibrosis; cirrhosis; hepatocellular carcinoma (cancer) and portal hypertension. See chapter 9.

Heart problems

Various types of cardiomyopathy (heart failure) and cardio-megaly conditions occur. These include cardiac arrythmias (irregularities of the heart beat) and ventricular dysfunction. These conditions usually occur in a younger person when iron levels are grossly elevated over a prolonged period of time. Echocardiography in early stages of the disorder can detect the presence of inter-ventricular septal thickness that reflects iron deposition. Some improvement in these conditions usually occurs when iron stores are reduced. See chapter 10.

Joint and bone problems

Osteoarthritis; synovitis (painful swelling of a joint); osteo-necrosis; chrondrocalcinosis; osteoporosis. See chapter 11.

Skin colouration and conditions

Bronze pigmentation occurs because iron builds up within and around the sweat glands. This causes an increase in iron in the epidermis. If the sweat glands are affected it can cause heavy, dark staining with a particular colour. Old scars can be highly pigmented,

and the conjunctiva and lid of the eye can be coloured. If the skin is heavily affected it can become a slate grey in colour. Fine skin is noted with diminished facial, pubic and axillary hair. There can be dryness associated with itchiness to varying degrees.

Diabetes mellitus

See chapter 12.1.

Hypogonadism (diminished sexual function)

This can cause reduced sex drive, cessation of menstruation (periods) in women and impotence in men. See chapter 12.2.

Hypothyroidism

Iron affects the thyroid gland and causes hypothyroidism, which slows down the body processes. Weight gain and tiredness are some of the signs of this problem. If tiredness is persistent after removal of iron this disorder should be considered. Treatment for these problems varies and can include hormone replacement therapy. See chapter 12.4.

Abdominal pain

Abdominal pain is a frequent complaint and may be described as an aching to a moderate pain sensation. The abdominal pain is located in the right upper quadrant, just above the stomach. Chest and back are occasionally also sites of pain. Often no cause is found, or it can be related to liver damage.

Mood swings

Systemic/non-specific problems

Fatigue, malaise and weakness

See Chapter 12.5.

2.3 Incidence of Complications

A survey of the members of the British Haemochromatosis Society showed the following percentage of members suffering complications:

Arthritis and joint pain	72%
Chronic fatigue	57%
Chest pains, cardiomyopathy, shortness of breath	53%
Mood swings, depression and anxiety	52%
Impaired sexual function	42%
Skin tan or grey colouration	34%
Abdominal pain	27%
Loss of body hair	25%
Liver disease	23%
Menstrual problems (% of women members)	15%
Diabetes	13%

2.4 Mortality

Deaths due to haemochromatosis occur mainly as a result of major organ damage. The most common causes are liver cancer, cirrhosis of the liver and pneumonia.

2.5 Factors that Influence Iron Overload

Age, intake of iron-rich food (especially red meat), intake of alcohol or other enhancers of iron assimilation (including vitamin C), intake of iron supplements and blood transfusions all tend to increase iron overload.

Gender dependent iron loss (menstruation and childbirth), blood loss and blood donation all tend to reduce iron overload.

2.6 Four Stages of Haemochromatosis

Haemochromatosis develops slowly. Even among those who have a genetic predisposition it may not develop at all. However, if it does, it normally progresses through four stages:

Stage 1	The genetic predisposition but no other abnormality (gene positive).
Stage 2	Iron overload but without symptoms (gene positive, elevated transferrin saturation and normal or elevated serum ferritin).
Stage 3	Iron overload with early symptoms (gene positive, elevated serum ferritin, fatigue and joint pain).
Stage 4	Iron overload with organ damage, especially cirrhosis.

2.7 Summary

A considerable quantity of iron may have accumulated before haemochromatosis is diagnosed. Anything over 4g of storage iron is considered to be a significant iron overload. Storage iron is iron stored in the tissues, particularly the liver, in the form of the protein ferritin, and its insoluble derivative, haemosiderin.

The earlier iron overload is discovered, the less will be the possibility of complications. The majority of affected individuals will not develop symptoms of iron overload or organ damage until the 4th or 5th decade of life. If levels are grossly elevated then substantial damage may have occurred.

Iron in the body is necessary for all aspects of bodily functions, but too much is toxic and may cause cancer.

3. GENETICS (INHERITANCE)

This chapter explains the basics of how the HFE gene, which controls iron overload, is passed from parents to children. It is a simplified account. In particular it is written as though there were only one possible mutation of the HFE gene, and that the gene is either normal or has a mutation. In fact, as explained in Chapter 1, there are three known variants – C282Y, H63D and occasionally S65C. However, the large majority of haemochromatosis sufferers will only be concerned with the C282Y mutation and the principles hold good in more complicated cases.

The chapter explains how inheritance works for genes, such as HFE, that have two particular characteristics called autosomal and recessive. These are explained below.

3.1 Terms

DNA

This stands for Deoxyribonucleic Acid. It is the genetic material of all living organisms. It carries all the genetic information that is needed in the form of a variation in molecular structure.

Chromosome

A chromosome is composed of DNA in a thread-like structure. An individual's genetic information is distributed along the length of his/her chromosomes. The genetic information may be regarded as subdivided into very short lengths, each of which constitutes a gene. Chromosomes come in pairs. Humans have 23 pairs: 22 homologous pairs, and 1 pair of sex chromosomes (X and Y). The genes on one of the pair are derived from the father: those on the other are derived from the mother.

Gene

A gene is a subdivision of a chromosome. It forms the basic unit of genetic material. Each person has about 20,000 to 25,000 genes. Usually a gene can be associated with a particular feature or characteristic that is inherited.

Autosomal gene

An autosomal gene is any gene on a chromosome that is not a sex chromosome, so it can affect men and women.

Recessive gene

Hemochromatosis is an autosomal recessive disorder. A gene is recessive if it only causes a particular characteristic to develop when it is present in both of the pairs of an individual's chromosome.

Mutation

A mutation is a change in a gene. Many changes do not cause problems and are more properly referred to as "variants". Haemochromatosis is an example of a problem caused by a mutation. When a mutation occurs it is permanent and will be passed from parent to children through the generations of a family. The mutation for haemochromatosis is said to have occurred 2,000 - 6000 years ago. This is a relatively young mutation in evolutionary terms.

HFE gene

The HFE gene is one of the genes that controls iron absorption. HFE is not an abbreviation; it is a label for the gene.

Three mutations of the HFE gene are found in the general population: C282Y, H63D and, more rarely, S65C. In Ireland 1 in 5 people are carriers. The mutation predominantly involved in iron overloading is C282Y.

About 12% of people of European origin are carriers (i.e. have one copy) of C282Y, about 25% are carriers of H63D and 2% of S65C. The C282Y mutation is often described as a “Celtic mutation” originating in a Celtic population in central Europe and spreading west and north by population movement. It has also been suggested that Viking migrations were largely responsible for the distribution of this mutation. However the HFE C282Y mutation may have occurred in mainland Europe before 4,000 BC and moved into the north and west of Europe as the ice retreated and people occupied the land.

Homozygous (2 mutated genes)

Let us call a gene that has a particular mutation the H gene and an unmutated gene the n gene. An individual is homozygous if they inherited an H gene from each parent, one on each part of the chromosome pair, making two abnormal genes, shown as HH. A person who has two H genes has the potential to develop a disorder associated with the mutation. A person with two H genes will always pass on an H gene to each of their children. (See Section 3.2)

Heterozygous (1 mutated gene)

An individual is heterozygous if the genes in the gene-pair differ, ie one is normal, n and the other mutated, H. If the mutation is recessive then the genetic disorder is usually asymptomatic (does not cause any symptoms). The individual with the Hn gene pair is said to be a “carrier” for the H mutation.

Compound heterozygous

Individuals who are compound heterozygous for the HFE gene have one HFE gene that is C282Y mutated and the other that is H63D mutated. This combination has the potential to develop iron overload.

3.2 Chances of Passing on the C282Y HFE Gene Mutation

Every person has two copies of the HFE gene, one copy inherited from their mother and one from their father. Each copy may be either normal, shown as n, or may have the C282Y mutation, shown as H. So each person can have 3 possible combinations for their HFE gene.

nn

Both copies of the gene are normal.
This person does not have the mutation.

Hn

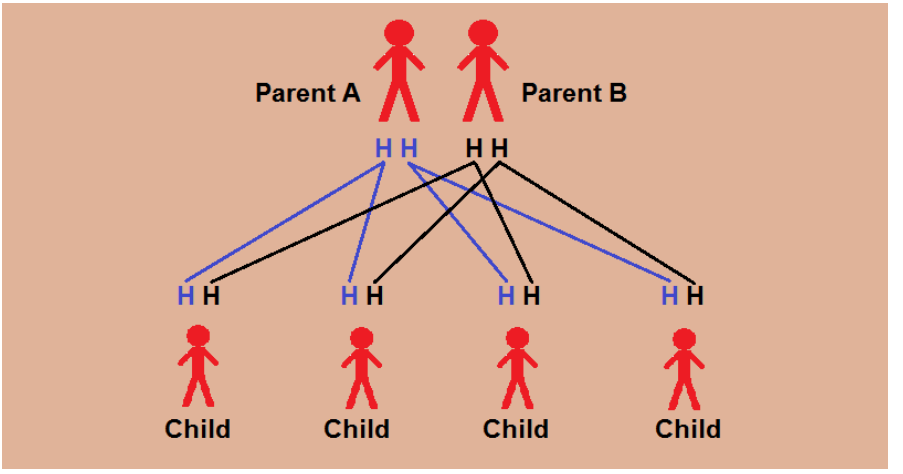
One copy of the gene is normal and one has the mutation. This person is called *heterozygote* for the HFE gene and is a carrier. He/She is unlikely to develop iron overload but may pass on a mutated copy of the gene to a child.

HH

Both copies of the gene have a mutation. This person is *homozygous* for the HFE gene. He/She will be at increased risk of developing iron overload and will definitely pass on a mutated copy of the gene to all children.

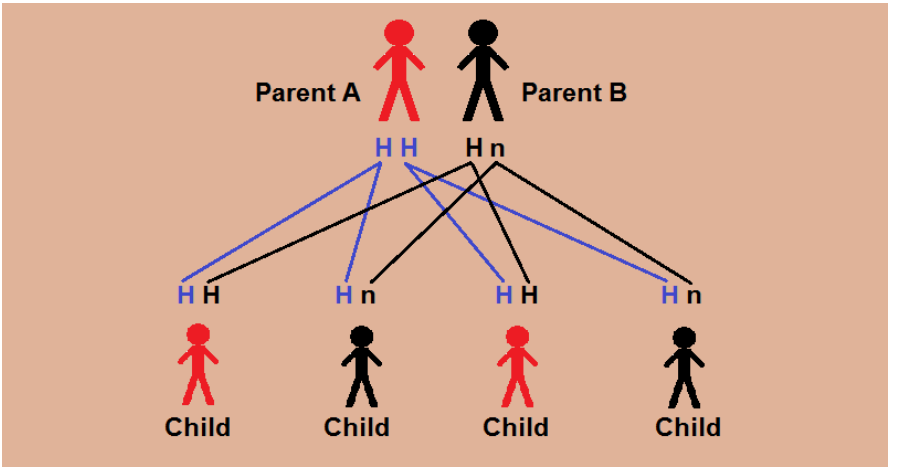
At conception each parent passes on one copy of the gene to the child, so the child has two copies, one inherited from each. The chances of a child inheriting the gene are as follows:

Possibility 1



Children will inherit an H copy from each parent, so all children will be HH.

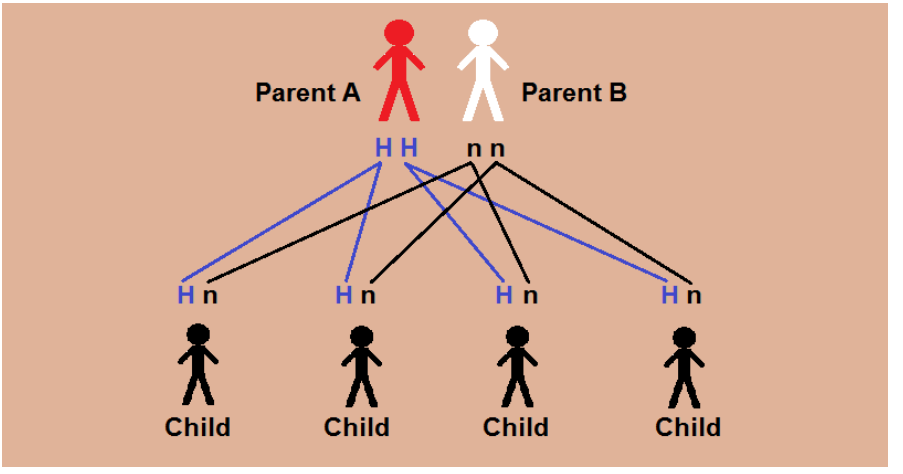
Possibility 2



Children will inherit an H copy from parent A and will have a

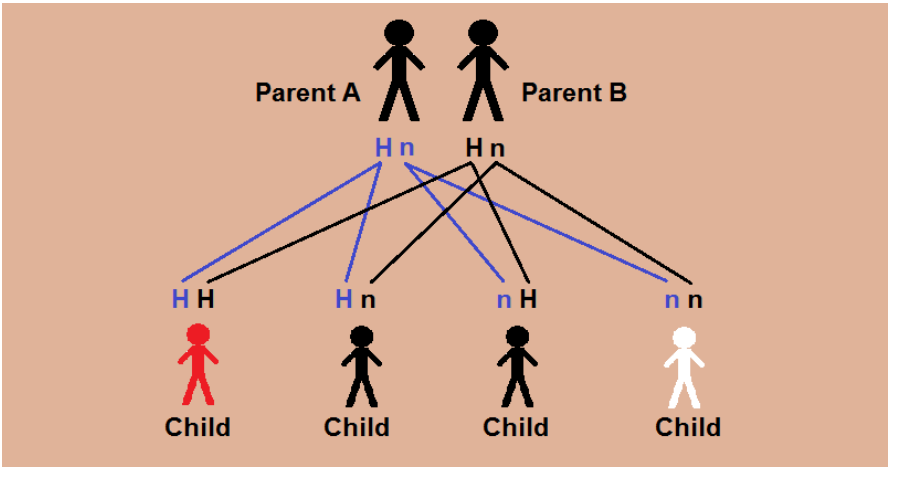
50% chance of inheriting an H or an n from parent B, so will have 50% chance of being HH and 50% chance of being Hn.

Possibility 3



Children will inherit an H from Parent A and an n from parent B, so all children will be Hn (carriers).

Possibility 4



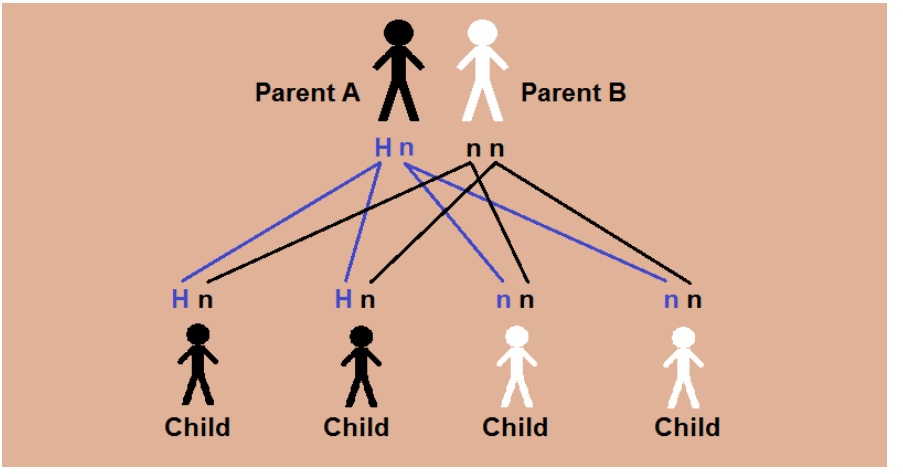
Children will have a 50% chance of inheriting an H from parent A. Those who do will all have a 50% chance of inheriting an H

from parent B and thus being HH, and a 50% chance of inheriting an n from parent B, and thus being Hn.

Children will also have a 50% chance of inheriting an n from parent A. Those who do will have a 50% chance of inheriting an H from parent B and thus being Hn and a 50% chance of inheriting an n from parent B and thus being nn. Combining these possibilities, the chances for children of these parents are:

HH 25%	Hn (carrier) 50%	nn 25%

Possibility 5



Children will have a 50% chance of inheriting an H from parent A and a 50% chance of inheriting an n, and they will all inherit an n from parent B, so they will all have a 50% chance of being Hn and a 50% chance of being nn.

These figures are probabilities; they show how inheritance will work out on average. This is because an Hn parent is on average equally likely to pass on an H or an n gene on any occasion. For any particular family the outcome may depart from

the average, for example all the children of two particular parents in Possibility 4 might be HH.

3.3 Family Health Tree

The information that determines how our bodies grow, develop and work, e.g. regulate iron absorption, is passed down through the generations by our genes. Any change in that information (a mutation in a gene) may also be passed down; thus conditions such as haemochromatosis “run in families”.

We can see how haemochromatosis has been inherited in a family by drawing up a family health tree. Many people investigate their family history to determine their roots, and if that search is extended to include health information, it may be possible to determine if a person is at risk of developing the disorder. The family health tree can be taken to a GP as an aid in early detection and prevention.

If any person on the tree has been diagnosed with haemochromatosis, this should be recorded. However, in many cases symptoms of haemochromatosis, such as are listed in this book, may have been present without being diagnosed.
It is important to talk to family members so that everyone can work together towards early diagnosis when the condition is present in a family. Once a case of haemo-chromatosis is diagnosed, all adult blood relatives should be informed and recommended to consider testing. It is also a good idea for the other partner to be tested.

4. TESTS AND DIAGNOSIS

Investigation for a possible diagnosis of haemochromatosis is likely to involve separate tests of whether the individual has iron overload, whether he or she has a gene mutation and whether he or she has suffered damage to the liver.

4.1 Tests for Iron Status

Serum ferritin (SF) is a measure of a protein called ferritin circulating in the blood serum. In healthy people it is a good indicator of the total amount of iron stored in all body tissues and it is the principal measure of iron overload. However, ferritin concentrations also increase as a result of infection, inflammation or liver disease as well as haemochromatosis. For every 1 µg/l (microgram per litre) in the SF level it is estimated that about 10 mg (milligrams) of iron is stored in the body. So, for example, an SF level of 1000 µg/l implies around 10,000 mg (that is 10 g) of stored iron.

Transferrin is the iron transport protein in serum. It carries iron from the gut around the body. **Transferrin saturation** (TS) is a measurement of the amount of iron that transferrin can bind and transport in the serum. A transferrin saturation result >45% is strongly suggestive of Haemochromatosis and should prompt a genetic test.

Haemoglobin (Hb) is the oxygen carrying pigment of the red blood cells. Hb contains iron, which acts as a “magnet” and draws oxygen to be transported to the cells and tissues. The measurement of Hb is probably the single most useful test during venesection therapy and should be taken either before or after treatment. The Hb should be kept above 11.5 g/dl (grams per decilitre) (females) or 13 g/dl (males). At lower values

anaemia occurs, and tiredness and weakness may be experienced.

When starting venesection the Hb level can be an indicator of iron levels falling too rapidly. If Hb falls too low, stop venesection until it recovers. Discuss this with your doctor.

You may have your tests (SF, TS and Hb) carried out on blood removed at the same time as venesection. This reduces the number of needle punctures needed and helps to preserve your veins. If you are experiencing any problems contact your doctor immediately. (See Chapter 5)

4.2 Normal Range for Iron Levels

	Males	Females
Serum ferritin - µg/l	15 - 300	15- 200
Transferrin saturation - %	16 - 50	16 - 45
Haemoglobin - g/dl	13.0 - 16.5	11.5 - 15.5

Iron overload resulting from haemochromatosis can raise the serum ferritin level to 6000µg/l or more. An Hb level below 13 g/dl (males) or 11.5 g/dl (females) is considered to be anaemic. Note that measurements can vary from laboratory to laboratory, so check your results against the normal ranges given with the pathology results (See Section 6.2).

4.3 Gene Test

If the SF and TS levels are persistently high, i.e. above the normal range given above, then further investigation such as the HFE gene test is warranted. A positive HFE gene test enables a confident diagnosis of haemochromatosis to be made. Approximately 5% of people with iron overload lack changes in

the HFE gene that can explain their iron overload. If iron overload has been demonstrated but there is no mutation of the HFE gene, other genes may be tested (see chapter 1.2).

It is not recommended to carry out genetic testing in children as iron overload does not normally develop during childhood. Testing should be delayed until they are able to understand the reasons for the test and to give consent (usually age 15).

4.4 Biopsy

A liver biopsy may be taken to reveal the health of the liver. If the serum ferritin is below 1,000µg/l and liver function tests (see chapter 7.2) are normal and there is no sign of hepatomegaly (liver damage), then a liver biopsy may not be needed.

4.5 Non-Invasive Tests

A form of magnetic resonance imaging (MRI) scan called FerriScan is coming into use as an alternative to liver biopsy but is only available at a few hospitals in the UK. Liver transient elastography (Fibroscan) is similar to an ultrasound scan and is more widely available. This test is being increasingly used to detect or exclude more severe forms of liver damage such as cirrhosis.

5. VENESECTION

The treatment of choice, and by far the most effective, is removal of blood, known in the medical world as venesection or phlebotomy. It is very like giving a blood donation. Each 450ml of blood contains about 200mg (1/5 of a gram) of iron. The body quickly makes new blood to replace the blood removed and uses iron from the body's iron stores to do this. Repeated venesection thus reduces the amount of iron stored in the body. It may take 1 or 2 years to remove 10g to 20g of excess iron.

A venesection, including a rest period after the blood removal has been completed, usually takes less than an hour. It is usually done in a hospital.

5.1 Phases of Venesection Treatment

There are two phases in the treatment.

Iron Removal phase. The objective in this phase is to reduce SF to less than 50µg. Some specialists are happy with 50-100 µg/l. While the guidelines do not prescribe a target for TS some haematologists seek to reduce this to 30%.

Maintenance phase. The objective of this phase is to maintain the SF in the range 50 to 100µg/l. Typically, maintenance requires 2 to 4 venesections a year.

5.2 Iron Removal Phase

The aim of venesection is to reduce the SF to less than 50µg/l (which is towards the low end of the normal range) without

inducing anaemia. The current view is that the sooner iron is removed, the better the prognosis for the patient. Venesection should take place weekly (or even twice weekly) until the SF concentration has been reduced to 50µg/l. If anaemia develops the rate of venesection should be reduced, initially to once a fortnight. Juveniles, adolescents and pregnant women may require a specially modified treatment schedule.

Each individual's medical practitioner adjusts the amount of blood removed for each individual. It can range from 200ml to 500ml at each venesection but 450ml is the most common. In individuals with a very high SF level it takes a long time to reduce the level since venesection cannot be tolerated more than twice a week. There may even be an increase in the level sometimes; do not be concerned by this, as over time there will be a reduction. It is not necessary to check the SF level too often in the early stages of iron removal, checking at monthly intervals is good enough. When the level nears 100µg/l, then check weekly.

Although there are variations between individuals you can get a rough idea of how many venesections are likely to be required to reach the target SF level of 50µg/l. Each venesection of 450ml of blood will remove about 200mg of iron, and this should in due course reduce the SF level by about 20µg/l. So to reduce the SF level from 1000 to 50µg/l would be likely to require about (1000 - 50) ÷ 20 venesections, that is about 50 venesections. However, this may be an under-estimate because it does not allow for continued absorption of iron from food during this time.

5.3 Maintenance Phase

After the serum ferritin level has been reduced to the target level regular maintenance venesection therapy should continue to keep the serum ferritin level in the range 50-100µg/l.
The frequency of maintenance venesection therapy required will be assessed individually. Periodic blood tests should be done to check SF and Hb level and some haematologists also continue to monitor TS. The combination of results together with how the individual feels will indicate when the next venesection should be carried out; a frequency of 2 to 4 times a year is the common range. Treatment for Haemochromatosis is ongoing for life. It is important that you go for regular check-ups with your GP.

5.4 Chelation Therapy

There are drugs that will remove iron from the body (called *chelation therapy*) and these are used to treat iron overload caused by the multiple blood transfusions necessary for the treatment of inherited anaemias. The most common chelating drug, desferrioxamine, is less effective than venesection and must be administered by continuous infusion, which is not pleasant for the patient. Although oral iron chelators are being developed venesection remains more effective and is therefore the preferred treatment for haemochromatosis.

5.5 Effect on Symptoms

At the same time as iron levels fall there will be a degree of improvement in some symptoms. This recovery period varies, and in some cases it can take a number of months before any change is seen. Some symptoms improve more than others, and effects vary between patients.

The table overleaf sets out the percentage of members of the Haemochromatosis Society experiencing changes in their symptoms after venesection treatment. These figures are based on the results of a survey conducted in 2005.

Symptom	Better	Unchanged	Worse
Arthritis	16	34	57
Chronic fatigue	58	28	14
Impaired sexual function	15	57	28
Chest pains, cardiomyo-pathy, shortness of breath	49	33	18
Skin colouration	42	54	4
Abdominal pain	59	28	13
Loss of body hair	0	72	28
Liver disease	49	46	5
Diabetes	29	50	21

Source: The Haemochromatosis Society survey of members 2005

6. MANAGING YOUR VENESECTIONS

6.1 Ask Your Doctor

Ask your doctor to explain your venesection goals. They should list the target levels for Serum Ferritin (reduce to and stay within a set range), Transferrin Saturation (the level to reach and what it means if elevated) and Haemoglobin (what is an acceptable level and what to do if it falls below that level). Ask your doctor to write these goals down for you.

6.2 Manage Your Own Records

Keep a record of your blood test results. Members of the IHA receive a booklet for this purpose from the Association. Make arrangements with whoever does your venesections about how best to obtain your results on a regular basis.

Check for yourself that your treatment is in line with the goals set by your doctor. Do not assume that someone else will always monitor your blood test results.

6.3 Lifestyle

Some people find venesections cause them no difficulties; some find them more of a problem. General lifestyle suggestions which may help include:

- Routine light exercise, say 20 to 30 minutes' walk 3 times a week.
- Plenty of fluid, a total of about 2 litres a day made up of water, tea, coffee and other drinks.
- Avoid alcohol in excess, i.e. not more than 3 standard drinks a day.

- Vitamin supplements may be included, e.g. B complex, folic acid, B12 (but not vitamin C or iron supplements), but check with your doctor the amount of any supplement to take.

- Wait until at least two days after treatment before undertaking vigorous activities.

6.4 Helpful Hints

Before venesections

- It is helpful to know what to expect during the venesection procedure. Do not feel embarrassed to ask if it is your first venesection.

- Drink lots of water and fluids (not alcohol) before appointment time. The increased fluid intake assists in a better flow of blood at the time.

At the time of venesection

- Tell your venesector if you have another medical condition or are taking medication.

- If your veins are difficult to access then a hot pack or some pumping up of the cardiovascular system by vigorous exercise may be beneficial. A brisk walk for 10 minutes or climbing a flight of stairs before treatment works well.

- For people who have a problem with the pain of a needle being inserted into a vein, application of a cream containing a local anaesthetic will numb the skin after 1 hour and last up to 5 hours. If you feel a need for it ask your treatment centre whether they can provide it. On

prescription it is lignocaine, over the counter it is EMLA cream.

- Some people have veins which are larger and easier for venesection than others. Small veins may be more easily accessed if two tourniquets are applied. Place one tourniquet in the usual place and one below the site. This creates a dam effect and the vein becomes full and easy to draw. Addition of a hot pack to the area may also be of assistance as this causes the vein to dilate. Discuss with whoever does your venesections.

After venesections

- Rest immediately after treatment for at least 15 minutes.
- Avoid smoking or drinking alcohol for at least an hour after treatment.
- If you feel faint tell someone and sit down straight away and put your head between your legs. If you fall you can cause yourself further injury.
- Keep an eye on the dressing for bleeding or unusual swelling or pain.
- The dressing may need to be left on for 8 hours.
- In hot weather have an extra dressing in case of leakage from the puncture site.
- Avoid carrying heavy objects with the arm for 24 hours.
- Eat regular meals and increase fluid intake to 2 litres per day. In hot weather drink extra fluids.

- Some people find that high protein drinks help with the persistent weakness that may occur with venesection therapy.

6.5 Complications that May Occur

Different people react differently to venesection.

- Some people may have psychological problems due to the trauma of having an invasive procedure. These should decrease with time. Assistance can be sought from the IHA.
- Fatigue can be a constant problem for some people. If fatigued, do not push yourself. It is better to rest.
- If anaemia occurs it is important to investigate and find the cause.

6.6 Communicate with Your Doctor

- Before you visit the doctor write down the important points you want to discuss and questions you want to ask.
- You have a responsibility to yourself to understand your medical problem, especially the purpose of any medication you may be asked to take by your doctor.
- Describe your health problems as accurately as possible. How long have you had them? What makes them better or worse?
- Write down the information your doctor gives you, including treatment and options.
- Consider asking to see a genetic counsellor if one is available in your area.

- If you need moral support during the consultation, ask a friend to go with you.

- If you are undecided about the tests or treatment your doctor is suggesting, take time to think it over. You have a right to ask for a second opinion.

6.7 Blood Donations

There are several ways that people with haemochromatosis can use the facilities of the Irish Blood Transfusion Service (IBTS). With the exception of point (4) below, the IBTS requires that you are in maintenance phase – needing to have a pint venesected at most every 3 months – before they start providing your therapeutic venesection service.

(1) If you are a regular donor who has donated blood within the past two years, and are otherwise well and are still eligible to donate blood for transfusion, and if you don't need more than four pints taken from you each year, you will be able to continue to go to regular blood donation clinics. This step probably only applies in practice to people who have been found to have haemochromatosis on family contact screening or general health screening. The IBTS does not monitor ferritin levels at regular blood clinics at present.

(2) If you live in the Dublin or Cork areas, or are happy to come to the IBTS clinics in Dublin or Cork, you can make an appointment at the haemochromatosis clinics in d'Olier Street in Dublin or St Finbarr's Hospital, Cork. These clinics are held every week, there's no charge whether you are eligible to be a blood donor or not, and there's no waiting list for an appointment. At these clinics the blood collected is not used for transfusion – but if you would like your blood to be considered for use for transfusion in hospitals you will be

assessed and tested for that at the clinic. If you are eligible, you will be able to donate blood as a regular donor in a regular blood donor clinic; if it turns out that you're not eligible then you will still be welcome back to the same clinic in Dublin or Cork for your treatment. (Remember that you can only have up to four pints taken each year - one every three months - at these IBTS clinics. This is enough for almost everybody once they have had their body iron stores returned to the normal range after diagnosis.) The IBTS does not monitor ferritin levels at these clinics at present. You'll need a prescription form from your doctor or nurse – downloadable from www.giveblood.ie/haemochromatosis.

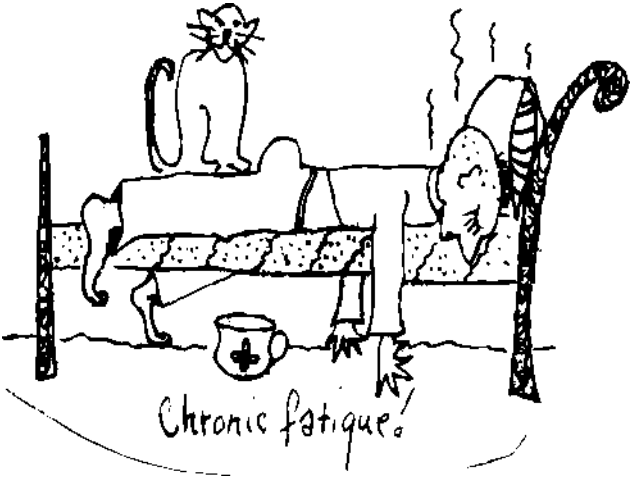
(3) There are plans to open a similar service based at University Hospital Limerick in 2016. Up-to- date information will be available on www.giveblood.ie/haemochromatosis.

(4) The IBTS runs a clinic for people with haemochromatosis who may need more intensive venesections every Friday in its facility in Stillorgan in Dublin. Access to this clinic is via referral from your GP, clinic nurse or consultant. It is only available to people who are eligible as blood donors and who have access to free venesection treatment – if you're not eligible then you are still welcome at the d'Olier Street clinic. The Stillorgan clinic can take more than four pints a year from donors, and measures ferritin levels regularly. This is a very popular service with donors and often does not have availability for new donors. The IBTS would like to increase this facility, and to provide it outside of this one location, but requires additional funding before it is able to do so.

6.8 Blood Transfusions

In any situation where you require a blood transfusion do not hesitate to accept a blood transfusion because you have haemochromatosis.

A haemochromatosis patient might wonder how much iron they would receive with blood transfusions. If bleeding is external and the transfusions are replacing lost blood then the net increase of iron will be negligible. If the bleeding is internal then there is the possibility that some of the iron contained in the blood lost from the circulatory system might find its way to the iron stores. This combined with transfusions could produce a net increase in iron loading. However, any extra iron can easily be removed by a few venesections at a later date.



Complications

7. IRON ABSORPTION AND BALANCE

Our food and drink contain iron and this is essential for normal function of body processes. Iron in our diet enters into the body through the gut. After a large loss of blood it takes 2 to 3 days for the body to respond to the reduction in iron that has taken place. So, if you give a blood donation, after a delay, absorption of iron from food and mobilisation of stored iron will both increase until the amount of iron taken out is replaced.

The delay between donation and increased iron absorption has to do with how the body sends signals to the small intestine and the growth and development of the intestinal cells. The removal of iron with blood taken in a venesection of a haemochromatosis patient produces a similar chain of events. The rate of absorption is different from one person to another, there is no way of predicting the rate for a person with iron overload.

7.1 Regulation of Iron

Iron is present in all tissues and cells. The iron not required by cells is stored as ferritin. The body closely regulates its absorption of iron so that its daily needs are met. The protein hepcidin is the mechanism by which this regulation is achieved, and the C282Y mutation causes iron overload by impeding the production of hepcidin.

If there is blood loss through haemorrhage or blood donation, the intestine senses this loss and increases the requirement so that the iron lost with the blood can be replaced. Blood creation can increase to 4 times the normal rate per day until the loss is replaced.

7.2 Loss and Replacement of Iron

Loss

You can only reduce stored body iron by blood loss. The body is made up of millions of cells and these cells have only a certain life span, after which they die. Dead cells are broken down in the body and some are excreted via faeces, urine and, for women, menstruation. Iron is also lost from the body surface where cells that die are discarded together with their iron content.

New cells are constantly being formed to replace those lost from the body. These new cells require iron and so take up the iron that is circulating in the blood stream.

The loss and replacement of iron is a continuous cycle within the body. Iron is present in the body in haemoglobin, myoglobin, cytochromes and in various enzymes involved in redox reactions. It is also stored as ferritin and haemosiderin in the liver and reticulo-endothelial system.

To achieve iron balance, absorbed iron has to match iron loss. Special allowance must be also made for the needs of growth, pregnancy and lactation.

Measured iron losses in adult males and post-menopausal women are about 1mg/day. Additional iron losses associated with menstruation vary, but a loss of 40mg of iron per cycle (averaged at 1.35mg/day) covers 90% of women. Thus, until menopause, the average rate of loss is just over 2 mg/day for women.

Replacement

The factors which determine the proportion of iron absorbed from food are complex. They include the iron status of an individual and the iron content and composition of a meal.

Depending on food intake, some 8-16mg of iron is normally present in the diet each day. 15% to 20% can be absorbed giving an iron absorption rate ranging from 1-3mg/day. Since the loss of iron is 1-2mg/day, dietary iron intake is capable of meeting all physiological requirements except at times of special demand.

Phases of rapid growth, such as early childhood and puberty, create peaks of iron requirement. This is a consequence of rapid expansion of the blood volume and the gain in body mass. Both factors are also operative in pregnancy. During the second and third trimesters, large increases in the blood volume of the mother and foetus accompany foetal growth and necessitate the absorption of an extra 1000-1300mg of iron. This translates into an extra 5-7mg of absorbed iron daily. Diet alone will not reliably meet the needs of all women and small supplements of iron may be necessary to maintain iron status.

7.3 Quantities of Iron

Assuming the weight of a person is 70kg, then the normal total body content of iron is 4g (4,000mg). This is divided as follows:

Haemoglobin	3g
Ferritin	about 0.5g
Myoglobin in muscle, cytochromes, and other proteins found in all tissues	0.5g

7.4 Iron Retention in Haemochromatosis

With haemochromatosis it takes many years for a significant iron overload to accumulate. The amount that will have accumulated when a patient reaches a particular age cannot be predicted because each person is different. Stored iron levels can exceed 50g. The aim of venesections is to reduce an individual's level to 1g. As explained in Chapter 5.2 removal of every 10g of iron is on average likely to require around 50 venesections.

7.5 Haemoglobin: Structure and Function

Haemoglobin is the oxygen carrying pigment of the red blood cells (erythrocytes). A lack of haemoglobin or red blood cells results in pallor and other symptoms of anaemia.

One haemoglobin molecule consists of four convoluted chains, each surrounding an atom of iron. Every red blood cell has 300 million haemoglobin molecules, each capable of holding four pairs of oxygen atoms. Iron is the oxygen magnet; it attracts oxygen to the red blood cell. As we breathe in, oxygen is taken up by red blood cells and transported to the tissues and cells of the body. This oxygen is utilised by the cells, then the waste product (carbon dioxide) is transported by the red blood cells back to the lungs and exhaled. This is the way in which oxygen is acquired by the body. It is called respiration.

Red blood cells are the most numerous cells in the body. In a tiny drop of blood there are 5 million of them. Every day a small proportion of red cells are lost by excretion, resulting in a loss of about 1mg per day. The replacement with new cells creates the demand for iron of about 1mg of iron per day, which is met by absorption from food. A disturbance in the balance between these processes can cause iron overload

7.6 Hepcidin

Hepcidin is now considered to be the principal hormone involved in iron regulation. Since its discovery in 2000, hepcidin has been a focal point of the iron research field, as it appears to be the master regulator of body iron levels, controlling how much iron is absorbed from the diet and how much is released from the body's cells.

People with haemochromatosis have low hepcidin levels; this is believed to be what causes them to accumulate more iron than is healthy. This hormone is primarily produced by hepatocytes (liver cells) and is a negative regulator of iron entry into plasma. Hepcidin acts by binding to ferroportin, an iron transporter present on cells of the intestinal duodenum. The loss of ferroportin from the cell surface prevents iron entry into plasma. **Decreased iron entry into plasma results in low transferring saturation, and less iron is delivered to the developing red blood cells (erythroblasts).**

Scientists believe that by finding a way to increase hepcidin levels or activity, they will be able to restore normal iron control to haemochromatosis patients.

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8. DIET AND HAEMOCHROMATOSIS

Iron overload cannot be corrected by control of the diet. Nor is it recommended that people with genetic haemochromatosis whose ferritin level has been satisfactorily lowered by venesection should attempt to rely on control of their diet to keep it at the desired level. There is a serious risk that a very restricted diet designed to stop iron absorption will in practice be lacking in other nutrients and will be damaging to overall health.

A healthy, varied diet is recommended. This is a diet that is based on grains, fruit and vegetables (including beans and pulses), and contains moderate amounts of dairy, meat and fish, or meat and dairy alternatives, including nuts. A healthy diet should be part of a healthy lifestyle, which should if possible include moderate exercise such as walking or swimming, and is necessary to maintain a healthy weight and enhance general well being.

While dietary control should not be used as the principal means to control iron levels simple dietary modifications can be used in conjunction with venesection to limit the re-accumulation of iron.

8.1 Dietary Iron: Haem Iron and Non-haem Iron

There are two forms of dietary iron:

- non-haem iron, which is found in cereals, fruits and vegetables, beans, pulses and nuts; and
- haem iron, which is found in meat, fish and meat products.

Non-haem iron contributes 90% of dietary iron intake in the

average Irish diet but accounts for a much smaller proportion of the amount absorbed by the body. Much non-haem iron is not absorbed because it is often found in foods that also contain components which inhibit its absorption.

The most important inhibitors are polyphenols and phytates. Polyphenols are found in fruits, vegetables and some beverages, notably tea, coffee and red wine. Some polyphenols have a stronger inhibitory effect than others. For example, tea polyphenols have a more inhibitory effect on the absorption of non-haem iron from meals than those in coffee. In Ireland, black tea (as opposed to green tea: it does not matter whether milk is added) is an important inhibitor because it contains high levels of polyphenols and is widely consumed.

Phytates are also strong inhibitors of the absorption of non-haem iron. Phytates are storage forms of phosphates and minerals, which are found in seeds, nuts, soya, wholegrain and unrefined cereals and cereal products.

On the other hand some dietary components, notably ascorbic acid (vitamin C) and alcohol, are strong enhancers of non-haem iron absorption.

Haem iron only accounts for approximately 10% of dietary iron intake in the average Irish diet. The absorption of haem iron is relatively unaffected by what is eaten at the same time. Therefore, haem iron is better absorbed than non-haem iron, and can account for half of the iron absorbed from the diet. Offal (liver and kidney) and blood products (black pudding) are particularly rich in haem iron, followed by red meat. White meat and fish contain less haem iron. In addition, protein components

contained in meat products and fish enhance the absorption of non-haem iron.

8.2 Changes of Diet to Reduce Absorption of Dietary Iron

If you want to reduce the amount of iron you absorb from your diet you might wish to adopt the following suggestions:

- Avoid consuming, or reduce your consumption of, offal and blood products, as these foods are rich in haem iron. You might also consider reducing your intake of red meat.

- Limit alcohol consumption with meals, since alcohol enhances the absorption of non-haem iron. More generally, alcohol is strongly discouraged for anyone with liver disease.

- Vitamin and mineral supplements and tonics containing iron should be avoided. Read the small print carefully as iron is often included even though it is not the main ingredient.

- Vitamin and mineral supplements and tonics containing vitamin C should be avoided, as vitamin C is a strong enhancer of non-haem iron absorption. Avoid regular consumption of fresh and concentrated fruit juices with meals as they contain high levels of vitamin C. However, it is important to consume fruit and vegetables as part of a varied diet.

- You may choose to avoid fortified breakfast cereals or only consume high-fibre (i.e. high phytate) cereals with milk

and tea and not with fruit juice. Read the ingredients carefully: many breakfast cereals have added iron.

- Drink black tea, with or without milk, at meal times to reduce the absorption of non-haem iron.

8.3 Raw Oysters and Clams

Raw oysters and clams may contain an organism named Vibrio Vulnificus. Iron is an important growth factor for Vibrio Vulnificus, therefore this organism multiplies rapidly in individuals with iron overload, and infection can be fatal.

For this reason, individuals with iron overload should not eat raw oysters or clams.

9. THE LIVER

The liver is the body's chemical factory and performs hundreds of complex functions that are vital for life.

9.1 Some Liver Functions

- Converts food into chemicals necessary for life and growth.
- Produces quick energy when needed.
- Manufactures new body proteins.
- Prevents shortages in body fuel by storing sugars, vitamins and minerals.
- Aids digestive process by producing bile.
- Controls the production of cholesterol.
- Digests fat.
- Neutralises and destroys poisons.
- Maintains hormone balance.
- Stores iron throughout life.
- Helps the body resist infection by producing immune factors.
- Regenerates its own tissue.

9.2 Tests to Determine the Health of the Liver

If liver damage is suspected the following tests are available to check the health of the liver:

- Liver function tests.
- Iron studies.
- Liver biopsy.
- Some imaging techniques such as magnetic resonance imaging (MRI) and computerised tomography (CT).

A diagnosis is based on the results of more than one test or technique.

9.3 Liver Function Tests

Liver function tests are blood tests used to assess the general state of the liver or biliary system. Few of these tests actually measure how well the liver and biliary systems are functioning, but they can indicate the presence of damage or inflammation. They are useful tools that provide information upon which a doctor can base the diagnosis and management of disorders of the liver and biliary system. However, interpretation of liver function tests is a sophisticated process. A doctor will be assisted by placing the results in the context of a patient's medical history, physical examination and other information.

Aminotransferases (ALT, AST)

The most commonly used indicators of liver damage are alanine aminotransferase (ALT) and aspartate aminotransferase (AST), formerly referred to as SGPT and SGOT.

These are enzymes that are normally found in liver cells. When liver cells are injured they leak out and make their way to the blood. ALT is the more specific indicator of liver inflammation as AST is also found in other organs such as the heart and skeletal muscle.

In acute injury to the liver, the level of ALT and AST may be used as a measure of inflammation or damage. In chronic liver disease this is not the case, for these enzymes are sometimes entirely within the normal range, even in the presence of cirrhosis.

Alkaline phosphatase (ALP)

Measurement of the ALP level is frequently used to detect obstruction in the biliary system. Elevation in the level of this

enzyme may be found in a large number of disorders including alcohol related liver disease, hepatitis and tumours.

Gamma glutamyl transpeptidase (GGT)

When the cause of the elevated ALP level is not clear, it is often useful to measure another enzyme, gamma glutamyl transpeptidase. Abnormalities of the GGT level suggest liver or biliary tract disease.

9.4 Tests to Monitor the Liver Once Damage has Occurred

The following tests and techniques are available:

- Blood test for Alpha Fetoprotein (AFP). This is a known marker for liver cancer.
- Ultrasound scan of the liver.
- MRI of the liver.
- CT scans of the liver with arterial and venous phases.

In patients with established cirrhosis or extensive scarring, screening for the development of hepatoma may be recommended. Many tests can evaluate the liver, including MRI and CT. However they are usually reserved for patients in whom there is a strong suspicion for the development of hepatoma. In all other patients with established cirrhosis screening is advised with abdominal ultrasound and AFP blood test every six months.

Obtain copies of your reports and if you have any questions raise them with your doctor. Good surveillance will detect new problems early and hopefully at a treatable stage.

9.5 Bilirubin

Bilirubin is the main bile pigment in humans. When elevated it causes the yellow discolouration of the skin called jaundice. Bilirubin is formed primarily from the breakdown of a substance called haem found in red blood cells. It is taken up from the blood, processed and then secreted into the bile by the liver. There is normally a small amount of bilirubin in the blood of healthy individuals.

An increase in the level of bilirubin in the blood results from either a rise in the formation of bilirubin (caused by the destruction of red blood cells) or a decrease in its removal from the blood stream (caused by liver malfunction).

A raised bilirubin level is not usually helpful in distinguishing between different liver diseases. It is, however, generally useful as a true test of liver function since it reflects the liver's ability to take up, process and secrete bilirubin into bile.

9.6 Blood proteins

Two other commonly used indicators of liver function are the level of albumin in the blood and the prothrombin time.

Albumin is an important protein, which is formed in the liver. Chronic liver disease causes a decrease in the amount of albumin produced, and therefore a reduction in the level of albumin in the blood. However, there are many other factors, which can affect this level.

The prothrombin time (PT) is a test to assess blood clotting. The PT is influenced by proteins made by the liver. When the liver is significantly injured, these proteins are not produced normally.

The PT is also a useful test of liver function since there is a good correlation between abnormalities in clotting measured by the prothrombin time and the degree of liver malfunction. PT values are usually measured in seconds and expressed in comparison to a control value.

9.7 Cirrhosis

Cirrhosis is a term doctors use to refer to a liver with lots of scarring. Scarring is caused by multiple different liver diseases including viral hepatitis, alcoholism and haemochromatosis. Cirrhosis can be diagnosed either by biopsy or by an MRI scan, and can also be suggested based on some findings on physical examination and abdominal ultrasound.

In the case of haemochromatosis, the scarring is caused by the build up of iron in the liver, which acts as a poison and injures normal healthy liver tissue. Fortunately cirrhosis is relatively rare amongst people with haemochromatosis and with greater awareness and earlier diagnosis of the condition it is hoped that it can be reduced further.

Unfortunately, cirrhosis will have occurred in the majority of cases in which haemochromatosis was not diagnosed until it had reached an advanced stage.

A patient with cirrhosis has a predisposition to primary liver cancer (hepatoma), a complication that is more often seen in older people. You can have liver cancer without cirrhosis. The treatment options for cancer of the liver are very limited.

Alcohol ingestion should be avoided if you have fibrosis or cirrhosis of the liver.

9.8 Hepatomas (Hepatocellular Carcinoma)

The long-term storage of a large amount of iron in the liver, as may occur as a result of haemochromatosis, can cause inflammation which leads to scarring, i.e. the onset of cirrhosis (see section 9.3). The inflammation and scarring increase the risk of the occurrence of a malignant tumour in the liver called hepatoma (liver cancer).

The increased risk also applies to people with damaging liver conditions other than haemochromatosis, e.g. cirrhosis caused by chronic viral hepatitis or excessive alcohol consumption. In the case of haemochromatosis, hepatomas may develop in up to 30% of patients with cirrhosis. Most cases of hepatoma require the previous development of cirrhosis of the liver.

This emphasises the importance of early diagnosis of haemo-chromatosis and the screening of relatives of diagnosed patients. The tendency to develop a hepatoma increases with age.

Hepatoma is curable only when diagnosed at a very early stage and the liver is surgically resectioned or transplanted. Chemotherapy and radiotherapy and other treatments may slow down its rapid growth but they are not cures.

A definitive cure depends on early diagnosis and complete removal of all malignant cells. For this reason all patients with liver damage due to haemochromatosis and other forms of chronic cirrhosis have to be regularly screened for the appearance of this highly malignant tumour, e.g. every six months. Ultrasound scan, CT scan and magnetic resonance imaging may detect hepatomas with a size of 1cm when they are easier to treat and less likely to have spread.

9.9 Blood test for Hepatoma

There is a simple blood test that may detect the presence of a hepatoma at a very early stage of its development.

Alpha Fetoprotein (AFP) is a protein of the blood formed primarily during foetal life. A few weeks after birth the levels of AFP decrease rapidly and remain very low for the rest of our lives. Despite the fact that AFP was discovered in 1956 as the main protein circulating in the blood of foetuses, we still do not understand its functions completely.

The liver and the gastro-intestinal tract produce AFP. It may be normally elevated in the blood of new-borns for the first weeks of life and in pregnant women because it may cross to the mother from the baby.

In adults the blood levels of AFP should always be below 50ng/ml (nanograms per millilitre). This is because normal liver and gastrointestinal cells produce very little AFP after birth.

In the process of liver cells turning cancerous, the cells grow more rapidly and become more disorganised; they go back to making AFP in large amounts. Even though we do not understand completely the mechanisms by which cancer cells resemble foetal liver cells in the production of AFP, we take full advantage of their effectiveness as a means of diagnosing hepatomas.

Very high levels of AFP are found in at least 70% of patients who develop hepatomas. Gradual increases in AFP in a person with haemochromatosis may indicate the onset of small hepatomas. Thus this test becomes an important tool for the early diagnosis and subsequent cure of these tumours.

As the tumour grows, the levels of AFP in the blood keep rising. Full-blown hepatomas cause levels that are frequently more than 1,000ng/ml. In general, the higher the level, the larger the tumour.

The test continues to be of help after the diagnosis. If surgery removes the tumour completely, AFP levels in the blood should return to normal within a week. Persistent elevation of AFP is a strong indication that some malignant cells remain in the body and that further treatment is required. Unfortunately, some hepatomas do not produce AFP and, therefore, cannot be diagnosed early with this method. Nevertheless, this simple blood test can permit early detection of a tumour and should be done routinely in patients at risk.

9.10 Portal Hypertension

Portal hypertension is a condition in which there is increased pressure in the blood vessels to the liver. It is associated with liver damage

10. THE HEART

If excess iron is allowed to build up in and around the heart it can damage the muscles of the heart (cardiomyopathy). This may occur of the serum ferritin is over 1,000 µg/l.

Symptoms can include:

- Arrhythmia or irregular heartbeat
- Breathlessness when more active than usual, or sometimes when resting
- Extreme tiredness and weakness
- Swelling in the legs, ankles and feet

Cardiomyopathy can lead to heart failure.

Up to a third of patients can be symptomatic. If you have any concerns about your heart whatsoever you should discuss this important subject with your doctor. Symptoms will often decrease when the excess iron has been removed but that does not remove the need for expert medical advice.

If you were already receiving medical treatment for a heart condition before you were diagnosed with haemochromatosis, tell your cardiologist about your haemochromatosis immediately. It may be that your haemochromatosis has been causing your heart problem, so your cardiologist needs to know about it.

11. JOINT DISEASE

Joint pain, stiffness and swelling are present in a high proportion of the people who have haemochromatosis. However arthritis in general is a common disease and is not specific for haemochromatosis in the population, so aches and pains in the joints of people with haemochromatosis may not necessarily be related to the genetic condition or to iron overload.

The cause of joint disease in haemochromatosis is not well understood. It may be due to calcium pyrophosphate crystals or even iron deposition causing progressive damage to the cells in the cartilage and joint lining. Unfortunately, venesection does not usually affect the development or progression of arthritis. Sometimes it is the presence of arthritis that leads to the detection of haemochromatosis; sometimes arthritis develops after haemochromatosis has been diagnosed.

There are two major types of arthritis - rheumatoid arthritis and osteoarthritis.

11.1 Osteoarthritis

Osteoarthritis is the most common type of joint disease and is due to wear and tear of the joint surfaces. It commonly affects the weight bearing joints (hips and knees) and can be effectively treated with joint replacement surgery. In haemochromatosis arthritis affecting the knuckles is relatively common. The arthritis that is recognised to be associated with haemochromatosis most closely resembles osteoarthritis, but in haemochromatosis it is distinctive in occurring at a younger age and involving some joints not usually affected by osteoarthritis, particularly the metacarpo-phalangeal joints in the hands and the ankles.

Arthritis in haemochromatosis patients also commonly affects the hips, knees and other knuckles in the hands.

11.2 Chondrocalcinosis

Osteoarthritis may be accompanied by the formation of crystals (calcium pyrophosphate) in the cartilage of a joint. These crystals can be seen on X-ray photographs as fine white lines or as having a cotton wool appearance. This condition is called chondrocalcinosis.

The condition is usually pain free, but can cause short episodes of acute pain and swelling within the affected joint. This is called an attack of 'pseudo gout' because what happens to the joint is similar to an acute attack of gout, but the cause is due to calcium pyrophosphate crystals and NOT due to urate as occurs in gout. These attacks are usually infrequent and may never occur. They are best treated by having fluid aspirated from the joint and steroid injected.

11.3 Treatment for Arthritis

Treatment is mainly to protect joints and ease symptoms, especially pain. Joint protection involves avoidance of overloading the affected joint, wearing appropriate cushioned shoes, orthotics, weight loss and exercises to improve muscle tone. Pilates, swimming, cycling and the cross trainer are all appropriate low impact ways of improving muscle tone and strength. Where necessary, aids may be provided by an occupational therapist to assist with grip, opening jars, dressing and other tasks. There are no drug treatments known to reverse the process of joint damage in patients with haemochromatosis, but a wide range of pain killing medications can be helpful including paracetamol, stronger

opioids, non-steroidal anti-inflammatory drugs and neuropathic pain killers such as amitriptyline. Joint injections are also used with good pain relief for several weeks or months in many patients. Joint replacements are the final intervention for patients with severe pain, and for the hip and knee are widely performed in all centers, and are generally very successful operations.

The development of arthritis can cause depression and change of life style. You can come to terms with this by developing a positive attitude and a good exercise programme.

11.4 Osteoporosis

Osteoporosis, which means “porous bones”, causes a loss of bone mass. This weakens the bones and makes them vulnerable to fracturing or breaking.

Osteoporosis becomes increasingly common as we get older, as part of the normal aging process, but it is accelerated in some people and is a common problem for women after the menopause. It does also affect men but less frequently. The condition involves a loss of bone density. It often affects the spine, causing shrinkage in height, a stooped posture and backache. It also is a common cause of fractures of the hip and wrist (radius).

Osteoporosis is more common among haemochromatosis patients than the general population. Usually patients present with this condition when their haemochromatosis is in the later stages. Though the association of haemochromatosis and osteoporosis is well established, it is unclear whether it is due to iron overload, hypogonadism (deficiency in sex hormones), liver disease or diabetes mellitus. However, in susceptible patients, only moderate iron overload appears sufficient to induce osteoporosis.

The likelihood of developing osteoporosis is reduced by adequate levels of Vitamin D, a calcium-rich diet and regular exercise.

Diagnosis is made by a bone density scan, or DEXA. Treatment includes tablets containing Vitamin D3, with or without calcium, and “bone sparing” medication such as bisphosphonates which reduce bone turnover and prevent further bone thinning. It is important to be screened for osteoporosis as early intervention with vitamin D3 can be effective in preventing progressive bone thinning with advancing years. If a fracture occurs then the stronger “bone sparing” medication is also used.

12. ENDOCRINE SYSTEM

The endocrine system consists of several glands and other structures. The glands are ductless; they secrete hormones directly into body fluids, mainly the blood. Hormones are carried in the blood stream to various organs of the body. Their role is to control and coordinate body functions.

Endocrine organs and structures which are potentially affected by haemochromatosis include:

Pancreas, resulting in diabetes

Pituitary Gland, resulting in

a) Gonadal failure (testes/ovary)
   - loss of libido
   - impotence
   - infertility/ loss of periods (amenorrhoea)
b) Osteoporosis
c) Anaemia
d) Hypothyroidism
e) Pituitary Failure

Gonads (testes/ovary), results as above but it is rare for iron to have a direct effect.

Thyroid Gland, resulting in Hyperthyroid (over active) or Hypothyroid (under active)

Bones, resulting in osteoporosis

Iron overloading is a very insidious disease causing effects throughout the body. If symptoms are displayed or complained of then testing for hormonal imbalances is warranted.

12.1 Diabetes Mellitus

Diabetes secondary to haemochromatosis is caused by or associated with the deposition of iron in the liver and the pancreas. This can lead to insulin resistance and glucose intolerance and to degenerative changes to the cells in the pancreas responsible for producing insulin.

Diabetes can often be diagnosed long before the detection of the haemochromatosis that may have caused it. Therefore it has been suggested that newly diagnosed diabetics be screened for haemochromatosis. However, the frequency of homozygosity for C282Y in patients with diabetes is little higher than the frequency in the general population. It seems that although haemochromatosis often gives rise to diabetes, haemochromatosis is not one of the major causes of diabetes because haemochromatosis is itself uncommon.

Conventional treatment for diabetes is diet, exercise, oral medication and/or insulin. Whether insulin or oral medication is required will depend on the degree of iron accumulation and the presence of liver cirrhosis. Treatment of haemochromatosis by venesection cannot reverse the damage to the cells in the pancreas. However, it can stop the progression of diabetes and there is evidence that it will allow approximately one third of patients on insulin to reduce their dosage.

12.2 Gonadal Failure

Hypogonadism is a condition in which the function of the ovaries and testes (gonads) is impaired. In haemochromatosis, hypogonadism in younger people invariably results in loss of libido. Menstruation in women can cease, and men can become impotent.

Sexual dysfunction associated with hypogonadism is the most common endocrine disorder in men with haemochromatosis. It occurs in 10-40% of male haemochromatosis patients, and is often an early symptom of the disorder.

In men, sexual impotency can be treated with testosterone replacement. Testosterone and similar steroid hormones are usually effective but should be avoided if the liver is damaged. In women, menstruation and successful pregnancy can be obtained with gonadotrophic and hormonal therapy.

12.3 Hypogonadism (males)

This is due to iron deposition in gonadotroph cells in the pituitary. It can lead to a reduction in testosterone and sperm production in the testes causing a loss of libido, partial/complete impotence, or loss of ejaculate.

Usually the condition does not respond to treatment. However, in patients with endocrine abnormalities of recent onset, venesections can restore pituitary and gonadal function. In addition to testosterone replacement, venesection therapy may also be of benefit.

12.4 Thyroid Disease in Haemochromatosis

Of the diseases of the thyroid, hypothyroidism (under-active thyroid) is more common in haemochromatosis than hyperthyroidism (over-active thyroid). Males are more susceptible than females. Hypothyroidism can be treated by administration of thyroxine.

12.5 Depression and Mood Swings

Excess iron can accumulate in the pituitary gland and cause hormonal imbalances. The disturbance to the secretion of hormones can interfere with behaviour in general, causing depression, producing mood swings, and stunting growth.

Depression and mood swings are frequently reported by members of the Haemochromatosis Society (see table in section 2.3), but there is little written about it in the medical literature.

13. ANAEMIA

13.1 Anaemia Associated with Haemochromatosis

Anaemia is a condition in which a person has a low haemoglobin (Hb) level, from whatever cause. The oxygen capacity of red blood cells does not fall in direct proportion to the Hb level, but it is certainly reduced in severe anaemia. The venesection therapy of a haemochromatosis patient may induce anaemia.

During venesection therapy the level of haemoglobin should be measured at least every second week. If it is low on two consecutive occasions, then a venesection should not be performed. It is possible to have a high serum ferritin level and a high transferrin saturation level at the same time as a low Hb level. The Hb level should be maintained in the range 11.5g/dl to 15.5g/dl for females and 13.0g/dl to 16.5g/dl for males. There can be variations in readings which your doctor will want to monitor.

13.2 Other types of anaemia

Anaemia may be caused by blood loss, acute haemorrhage, and chronic bleeding over a prolonged period of time. Anaemia occurs in diseases of the kidney, liver and spleen. Other diseases such as cancer, Addison's disease, leukaemia, copper deficiency, hook worms, iron deficiency, vitamin deficiency, radiation exposure, just to name a few, may cause various states of anaemia.

Most doctors prescribe iron supplements when the haemoglobin count is low. If you have haemochromatosis your doctor should be aware that you have the disorder and alert to the need to check iron levels before proceeding with the prescription.

Self-medicating with iron supplements is a dangerous practice.

Many multivitamins will contain iron.

The message is: do not take non-prescription iron supplements without having an iron test first. And do not medicate with vitamins and supplements unless you have a particular deficiency.

14. NEONATAL HAEMOCHROMATOSIS

Neonatal haemochromatosis is a rare condition characterised by heavy parenchymal iron deposition in several organs and irreversible liver failure at birth. The only therapeutic option used to be liver transplantation.

Some cases of neonatal haemochromatosis have been linked to a maternal factor, eg an antiribonuclear factor antibody. Infusions of gamma globulin in pregnancy appear to reduce the severity of the condition and it has been proposed that the disease is due to an alloantibody (like rhesus incompatibility).

HFE gene mutations have not been found for neonatal haemochromatosis.

15. JUVENILE HAEMOCHROMATOSIS

Juvenile haemochromatosis is extremely rare and, though similar in nature to (adult) haemochromatosis, it is genetically distinct. In most cases changes in the genes coding for hepcidin and hemojuvelin (chapter 1.2) appear to be responsible for iron overload.

If a youth presents with cardiac problems, endocrine problems, diabetes or arthritis, juvenile haemochromatosis should be considered. This type of haemochromatosis is a severe form of iron overload and should be treated vigorously.

Youths (juveniles - 6 to 12 age group - and adolescents - 13 to 17 age group) are at risk, especially an adolescent in a family with a history of cancer, heart disease, diabetes, depression, or cirrhosis.

A transferrin saturation (TS) test should be performed when a child or teenager is demonstrating symptoms associated with iron overloading. If the TS level is elevated then iron studies should be performed.

Both juveniles and adolescents may demonstrate elevated liver enzymes.

SOURCES OF ADDITIONAL INFORMATION

Haemochromatosis Societies

The Irish Haemochromatosis Association
www.haemochromatosis-ir.com
The (UK) Haemochromatosis Society
www.haemochromatosis.org.uk
The Haemochromatosis Society Australia Inc
www.haemochromatosis.org.au
Canadian Hemochromatosis Society
www.toomuchiron.ca
The Haemochromatosis Society of South Africa
www.haemochromatosisza.org
The Iron Disorders Institute (USA)
www.irondisorders.org

The European Federation of Associations of Patients with Haemochromatosis

www.efaph.eu

Detailed and specialised sources on Haemochromatosis and its treatment

European Association for the Study of the Liver, Haemochromatosis Guidelines
http://tinyurl.com/easlguidelines

Living with Hemochromatosis, Gregory Everson and Hedy Wineberg, A Healthy Living Book ISBN 1-57826-104-X
HFE mutations, iron deficiency and overload in 10,500

blood donors, H.A Jackson, K.Carter, C.Darke, M.Gutteridge, D.Ravine, R.Hutton, J.Napier, M.Worwood (2001) Brit Journal of Haematology 114,474-484
Only a small proportion of those with the mutation overload iron
Entry for haemochromatosis in www.orpha.net
A European database of rare diseases, in several languages
A novel MHC class 1-like gene is mutated in patients with hereditary haemochromatosis, J. Feder et al (1996) Nature Genetics Vol13, pp399-407
The identification of the haemochromatosis mutation
Features of Genetic Haemochromatosis in Women Compared with Men, R.Moirand et al (1997) Annals of Internal Medicine Vol 127, 105-110

Genetics and HFE gene mutation

Genetics: a beginner's guide Guttman, Griffiths, Suzuki and Cullis. One World, ISBN1-85168-304-6
More than a beginner's guide
The Origin and Spread of the HFE-C282Y haemochromatosis mutation, S. Distante, K. J. H. Robson, J. Graham-Campbell, A. Arnaiz-Villena, P. Brissot, Mark Worwood, Human Genetics (2004) *Conclusions of an expert conference*
Inherited iron overloading: genetic testing in diagnosis and management M Worwood (2005) Blood Reviews, 19, 69-88
Reports advances in understanding
Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force, Whitlock et al (2006) Annals of Internal Medicine 145(3) I18
Concludes that a case for population screening has not been established
Founder mutations, D. Drayna, Scientific American, 2005
An explanation of how mutations spread

Diabetes & Diet

Prevalence of hereditary haemochromatosis in late-onset type 1 diabetes mellitus: a retrospective study Ellervik et al (2001) Lancet Vol 358 1405-1409
Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis, J. P. Kaltwasser, E, Werner, K.Schalk, C.Hansen ,R.Gottschalk, C.SeidlGut, Vol 43, pp699-704

Many more papers on haemochromatosis have been published in specialist medical journals, which are written for medical professionals and not easy reading for lay readers. The list is very long but it provides an excellent starting point for information on recent findings. For more see www.goo.gl/8ZE1U

Further Support Groups*

Arthritis Care
0808 800 4050 | www.arthritiscare.org.uk
Arthritis Research Campaign
0300 790 0400 | www.arthritisresearchuk.org
Diabetes UK
0345 123 2399 | www.diabetes.org.uk
The British Liver Trust
0800 652 7330 | www.britishlivertrust.org.uk
The Sexual Advice Association
0207 486 7262 | www.sda.uk.net
National Osteoporosis Society
0845 450 0230 | www.nos.org.uk

**Note that some telephone calls may incur charges.*

Your Notes

Irish Haemochromatosis Association

Iron Overload

Supporting people with haemochromatosis

Promoting awareness among health professionals

Raising awareness of patients and their families, the general public and policy makers to encourage vital early diagnosis

Supporting research

Working with international partners to improve understanding

The Irish Haemochromatosis Association
The Carmichael Centre
North Brunswick Street
Dublin 7

Registered Charity CHY No 14876
Charities Regulatory No 20049737

Voice Mail: (01 873 5911
e-mail: info@haemochromatosis-ir.com
Website: www.haemochromatosis-ir.com

The Irish haemochromatosis Association is compliant with the Governance Code of Community, Voluntary and Charitable Organisations and is committed to the standards of the Statement of Guiding Principles for Fundraising.

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