What is Thalassaemia?

Thalassaemia is the name of a group of genetic, inherited disorders of the blood. More specifically, it is a disorder of the haemoglobin molecule inside the red blood cells. It is an inherited genetic disease i.e. a disease that is passed from parents to children through the genes (genetic). It is not infectious and cannot be passed on from one individual to the other by personal or any other contact, nor through blood, transfusion food or air. The two main types of thalassaemia are ß (beta) and α (alpha). Both affect the production of normal haemoglobin -a key constituent of human red blood cells. Other "abnormal" types of adult haemoglobin also known as Structural Haemoglobin Variants have been identified and these include: mainly: Haemoglobin S (HbS), Haemoglobin E (HbE), C, D and Lepore.

Structural Haemoglobin Variants can combine with ß-thalassaemia to produce other related clinically significant blood disorders including:

- Haemoglobin E (HbE)/ß-thalassaemia
- Hb Lepore/ß-thalassaemia
- HbS/ß-thalassaemia

The name thalassaemia

ß-thalassaemia. The name thalassaemia derives from a combination of two Greek words: *thalassa* meaning the sea, i.e. the Mediterranean, and *anaemia* ("weak blood"). ß-thalassaemia is also known as Mediterranean anaemia. Both of these names come from the fact that this disorder was first described in patients originating from countries around the Mediterranean and for many years the belief was that this was a disorder exclusively occurring in these countries. Another term found in literature, although infrequently, is Cooley's anaemia, in recognition of the contribution of Prof. Thomas Cooley, a paediatrician in the USA who first described the clinical characteristics of this disorder in patients of Italian origin in 1925.

Terminology

Individuals with or having the ß-thalassaemia/Mediterranean anaemia/Cooley's anaemia trait (sometimes called stigma) are referred to as having ß-thalassaemia minor, or being heterozygous for ß-thalassaemia, or simply as carriers of ß-thalassaemia. They are not patients but individuals who inherit a normal haemoglobin (β-globin) gene from one parent and the defective gene from the other parent.

Individuals with ß-thalassaemia major/Cooley's anaemia/Mediterranean anaemia are referred to as being homozygous for ß-thalassaemia. They are individuals who inherit both defective haemoglobin (ß-globin) genes, one from one parent and one from the other. These individuals are going to develop the full blown disease.

About carriers of the thalassaemia trait

Carriers of the thalassaemia trait do not have a disease. They have no physical or mental symptoms and do not require a special diet or medical treatment. The condition cannot become a serious disease over time – indeed, most will be unaware that they are carriers unless specifically tested. However, some carriers may experience mild anaemia, which may be inaccurately diagnosed as iron deficiency anaemia. Laboratory

tests can differentiate between the two. Pregnant women carriers may experience moderate anaemia which is addressed by prescribing iron supplements during pregnancy.

How thalassaemia is passed on from parents to children

The ß-thalassaemia trait is passed on from parents to children by an autosomal recessive pattern of inheritance. When a child is conceived, it inherits one ß-globin gene from each parent. When both parents carry normal or "healthy" haemoglobin (ß-globin) genes, the child will inherit two normal ß-globin genes.

When one of the parents carries an affected haemoglobin (ß-globin) gene, i.e. when he/she is a ß-thalassaemia carrier, and the other parent carries a healthy haemoglobin (ß-globin) gene, each child born to these parents has a one-in-two (50%) chance of inheriting the affected thalassaemia gene from the carrier parent. These children are known as:

- carriers of ß-thalassaemia
- individuals heterozygous for ß-thalassaemia
- individuals with ß-thalassaemia minor
- individuals with or having the ß-thalassaemia trait

When both parents are carriers, then each child born to these parents has a one-in-four (25%) chance of being healthy (without the thalassaemia gene), a one-in-two chance (50%) of being a carrier like its parents, and a one-in-four chance (25%) of having ß-thalassaemia major.

Finding out if you are a carrier of ß-thalassaemia

In most cases simple laboratory tests can identify whether a person carries the thalassaemia trait. However, before any laboratory tests are carried out, it is important that individuals receive genetic counselling where possible, providing them with information, advice and guidance on why they should be tested and what the results of the test will mean for them. Otherwise provision of this information should rely on a good health education programme. A genetic counsellor will be specially trained, able to discuss important aspects of prevention, but also of the disease itself including:

- where to be tested
- how to interpret test results
- what it means to be a carrier, including options available to two carriers planning to have children or who have already conceived – referred to as "at-risk" couples
- the nature and treatment of thalassaemia major or of any other haemoglobin disorder or genetic disease.

A counsellor should provide information to individuals and couples, allowing them to decide for themselves how they wish to proceed. However, the advice offered by a counsellor and the decision taken by the at-risk couple is often influenced by religious and cultural beliefs. TIF's publication *Prevention of Thalassaemias and Other Haemoglobin Disorders, Volume I* offers the reader more detailed information on these issues.

Laboratory testing to establish whether one is a carrier of the ß-thalassaemia trait

Laboratory tests for thalassaemia include a routine blood test known as a Complete Blood Count (CBC), which includes measuring the level of haemoglobin and other parameters related to the number and volume of red blood cells and concentrational Haemoglobin known as Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH) respectively. For example, in adults, an MCV of less than 75FL may be indicative of a carrier state (alternatively, it may indicate iron deficiency – a further test will establish which is the case). MCV levels may be lower in children and vary according to age. Red blood cells are also examined under a microscope in order to examine their size and shape. The red blood cells of a carrier of ß-thalassaemia will be a paler shade of red and be various shapes (poikitocytosis), compared to normal red blood cells which are a darker red and round and concave in shape.

If further laboratory tests (such as Total Iron Binding Capacity (TIBC) and ferritin) exclude iron deficiency as the cause of a lower MCV, additional tests are carried out to confirm the presence of the thalassaemia trait and to determine its type. Tests to determine the presence of the ß-thalassaemia trait include a process known as haemoglobin electrophoresis, which enables quantitative measurement of HbA and HbA2, the main and minor components of adult haemoglobin. Other haemoglobins normally present in adult red blood cells, such as foetal haemoglobin (HbF), may also be measured by electrophoresis. In most cases, the above tests are sufficient to determine whether an individual is a carrier.

The presence of the α-thalassaemia trait was in the past usually identified by a process of exclusion or deduction: people who have low MCV (not due to iron deficiency), a normal haemoglobin electrophoresis that does not identify the ß-thalassaemia trait, and who come from countries with high prevalence are presumed to be α-thalassaemia carriers. Nowadays advance laboratory technology such as HPLC provides accurate diagnosis.

In some circumstances DNA tests need to be carried out in order to determine the presence or absence of the ß- or α-thalassaemia trait. Such genetic tests are beginning to be more widely used to test for the thalassaemia trait.

Why it is important to know if you are a carrier

Although being a carrier of the thalassaemia trait has no adverse health effects, it becomes important if a carrier marries another carrier. This is what is referred to as an “at-risk couple”. For such couples there is a one-in-four (25%) chance in every pregnancy that the child will have thalassaemia major.

Other possibilities in couples include the following.

An individual with ß-thalassaemia major (homozygous) with a partner who is a carrier of ß-thalassaemia: one-in-two (50%) probability with each pregnancy that the child will be homozygous for ß-thalassaemia. One-in-four (25%) probability that the child will be “normal” and one-in-four (25%) probability that the child will have ß-thalassaemia major.

An individual with ß-thalassaemia major (Homozygous) with a “normal” partner: 50% probability with each pregnancy that the child will be carrier of ß-thalassaemia.

An individual with ß-thalassaemia major (homozygous) with a partner who is also homozygous for ß-thalassaemia: 100% probability that the child will be born with ß-thalassaemia major.

Abnormal haemoglobin

HbE/ß-thalassaemia

HbE is one of the most common abnormal haemoglobins, particularly amongst people of southeast Asian ancestry, such as Cambodians, Vietnamese and Thais. If one parent carries the ß-thalassaemia trait and the other parent carries the HbE trait, there is a 25% chance in each pregnancy that the child will be born with HbE/ß-thalassaemia.

HbE/ß-thalassaemia is a moderately severe anaemia whose symptoms are usually similar to those seen in ß-thalassaemia intermedia but which may be as severe as those seen in thalassaemia major.

Hb Lepore/ß-thalassaemia

A combination of Hb Lepore with ß-thalassaemia results in a severe clinical condition resembling ß-thalassaemia major and is inherited in the same way as the one described above for HbE/ß-thalassaemia. When one parent carries the ß-thalassaemia trait and the other parent the Hb Lepore trait there is a 25% chance in each pregnancy that the child will be born with Hb Lepore/ß-thalassaemia.

Sickle cell disease

Sickle cell disease can occur when an individual inherits the abnormal haemoglobin HbS from both parents or if one parent carries HbS and the other ß-thalassaemia.

Sickle cell anaemia is a serious inherited (genetic) disorder. People who have sickle cell anaemia are born with it. It is a lifelong disease in which the body makes abnormally shaped red blood cells. Normal red blood cells are smooth and round like a doughnut without a hole. They move easily through blood vessels to carry oxygen to all parts of the body. In sickle cell anaemia, the body produces red blood cells that are shaped like a sickle (or crescent). These "sickle cells" are hard and sticky and they don't move easily through blood vessels. They tend to get stuck and block the flow of blood to the limbs and organs. This can cause pain, organ damage, and a low blood count (anaemia).

Sickle cell anaemia affects millions of people. Effective treatments exist for the symptoms and complications of the disease, but there is no cure, although in selected cases bone marrow transplantation may offer a cure. Over the past 30 years, doctors have learned a great deal about the disease. They know what causes it, how it affects your body, and how to treat many of the complications.

α-thalassaemia

α-thalassaemia is very different from β-thalassaemia; There are over 260 million carriers of -thalassaemia in the world, with the highest incidence in India, Southeast Asia and Africa and, to a much lesser extent, in the Mediterranean region; it is very rare in northern Europe.

By contrast to β-globin, α-globin is made up of four genes, two on each strand of chromosome 16. The α-thalassaemia traits combine in different ways to produce blood disorders that range from mild to severe.

Hb Bart's hydrops foetalis syndrome is the most severe α-thalassaemia, the homozygous state for α^0-thalassaemia: All four α-globin genes are not functioning and no α-chains are produced. The condition causes severe anaemia leading to the death of the foetus.

HbH Disease is a disorders that has a wide variation in clinical outcome but individuals with HbH disease are in the majority of cases healthy with only a mild anaemia but in some cases the anaemia may be severe.

The importance of α-thalassaemia in the clinical course of β-thalassaemia is due to the fact that presence of the α-thalassaemia trait is important in patients with homozygous β-thalassaemia, as it can reduce the imbalance between the α- and β-chains and so produce a milder clinical outcome of β-thalassaemia.

Epidemiology of Thalassaemia and other Hb disorders

Thalassaemia was originally thought to be a disease limited to the Mediterranean region, however it is now known that it occurs widely throughout many parts of the world. Thalassaemia has been identified across southern Europe from Portugal to Spain, Italy and Greece, as well as in a number of central European countries and parts of the former Soviet Union. Thalassaemia also affects the Middle East through to Iran, Pakistan, India, Bangladesh, Thailand, Malaysia, Indonesia and southern China, as well as countries along the north coast of Africa and in South America.

Thalassaemia is particularly prevalent in areas in which malaria is or was once endemic. The malaria parasite is an infectious agent carried by the anopheles mosquito, enters the human body through a mosquito bite and causes disease in humans by attacking the red blood cells. It is thought that in areas where malaria was endemic, humans underwent a small genetic adjustment which gave them an advantage over those in whom this change did not occur. This is because important changes occurred in the environment of the red cells following this genetic change that did not allow malaria parasites to survive and multiply. This adjustment leads to β-thalassaemia minor or β-thalassaemia trait.

It is believed that carriers of the β-thalassaemia trait were better able to survive malaria than healthy individuals, the number of carriers increased significantly over the years in malaria-endemic regions of the world as large numbers of healthy individuals died as a result of severe malaria infection. Although malaria eradication programmes in recent years have led to a steep fall in the incidence of malaria in many parts of the world, tackling thalassaemia and other severe haemoglobin disorders nonetheless remains a considerable challenge.

Population migration and intermarriage between different ethnic groups has introduced thalassaemia in almost every country of the world, including northern Europe where thalassaemia did not previously exist and where now it is becoming a major public health problem.

While reliable sources estimate that about 1.5% of the global population – 80–90 million people – are carriers of β-thalassaemia, with about 60,000 affected children born annually, the great majority in the developing world, it is certain that coming updated figures will demonstrate that those are gross underestimates. There is still little accurate data available on carrier rates (gene frequencies) in many population groups, particularly in areas of the world known or expected to be heavily affected. According to TIF records, however, only about 200,000 patients with thalassaemia major are alive and registered as receiving treatment around the world – underlining the bitter reality that the majority of affected children, born in developing countries, die undiagnosed or misdiagnosed, receiving sub-optimal treatment or left untreated altogether.

The choices available for an "at-risk" couple – when both are carriers of β-thalassaemia

Prenatal testing

Where a woman carrying the β-thalassaemia trait is considering having a child or is already pregnant, her partner (if not aware of his carrier status) should be tested at once to find out if he also has the thalassaemia trait. If they are both carriers, the couple may decide to proceed with planning a family or, if already pregnant, may consider continuing the pregnancy and where this is possible, to proceed with testing the foetus for thalassaemia, possibly deciding to terminate pregnancy if the foetus is affected. Other choices considered by "at-risk" couples include separation, adopting, proceeding to in vitro fertilization with foreign healthy sperm or ova. Or parents mainly due to religious beliefs may decide not to find out the status of the child and continue with the pregnancy.

There are three types of tests that can determine whether an unborn child has thalassaemia:

(i) Amniocentesis

Amniocentesis is performed in the second trimester of pregnancy, after about 15 (18-22) weeks' gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother's abdomen to withdraw 2–3 tablespoons of amniotic fluid. The foetal cells (cells from the unborn child) present in the fluid are then analysed in the laboratory to determine whether the foetus has thalassaemia. This test is used when the pregnancy is far advanced. It poses no significant risk to the mother. However, the test may cause a miscarriage from a few days to a few weeks after the test.

(ii) Cordocentesis (sampling of foetal blood)

Under ultrasound guidance, a fine needle is inserted through the abdomen into the foetal umbilical cord. About 2–3 ml of blood is aspirated and foetal blood is separated out in the laboratory. In skilled hands 100% pure foetal cells are obtained from the first attempt in the majority of cases. Causes of failure in obtaining pure foetal blood include early gestational age, less than 18 weeks, maternal obesity and posterior placenta. Early gestational age is also the most important cause of occurrence of serious complications in cordocentesis.

Globin chain separation with gel electrophoresis is the usual laboratory method of detection. Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis which is now mainly indicated only in pregnant patients who report late, in those in whom CVS is inconclusive and when previous studies of at risk couples are not available.

(iii) Chorionic Villus Sampling (CVS)

CVS can be performed somewhat earlier than amniocentesis, at about 10–11 weeks' gestation. Using ultrasound as a guide, the specialist obstetrician removes a small sample of the chorionic villi – cells that contain the same genetic information as the foetus and which will eventually form the placenta. The cells are removed either by a thin needle inserted through the mother's abdomen (transabdominal) or a thin catheter inserted through the vagina (transcervical). The cells are then analysed and a diagnosis made. As with amniocentesis CVS poses no significant risk to the mother. However, there is again a small risk of a miscarriage. If a miscarriage does occur, it can be difficult to know whether it was due to CVS, because many miscarriages happen naturally at around 12 weeks of pregnancy.

There may be an increased risk of the baby's limbs being malformed if CVS is done very early in pregnancy -i.e. before the 8th week after the last menstrual period. However, there is no evidence of an increased risk of any malformation when CVS is carried out after the beginning of the 9th week after the last menstrual period. This is why the procedure is generally carried out after the beginning of the 10th week after the last period.

How genetic testing works

Amniocentesis and CVS are both based on DNA testing and involve identifying the genetic abnormality (mutation) present in parents – the most accurate means of diagnosing inherited diseases. However, as with all tests, there is a possibility of error, albeit a very small one.

The genes for the characteristics we inherit, including haemoglobin, are made of DNA. Every tissue in the body, including a baby's placenta, contains a person's entire DNA pattern. In the case of CVS, for example, laboratory scientists study the haemoglobin genes contained in the DNA of cells from the chorionic villi to see if the baby will be normal, a thalassaemia carrier or will have thalassaemia major. Analysis of the sample usually takes about a week.

Termination of pregnancy

If the test shows that the baby is affected, the couple may decide to end the pregnancy. The role of the genetic counsellor and the obstetrician in these cases is extremely important. Even at this stage a decision may be taken by the couple to continue with the pregnancy accepting the lifelong treatment of the affected child. If pregnancy termination is the choice, however, this is done in one of two ways, depending on the stage of the pregnancy.

Early termination

Early terminations can be carried out when a woman is less than 14 weeks pregnant. The couple should be informed that termination does not reduce the woman's chance of

having another baby. However, it should also be explained that each pregnancy conceived by an at-risk couple carries the same risk of producing an affected child. If the couple wishes to know whether any subsequent babies conceived carry thalassaemia, prenatal diagnosis will have to be carried out again.

Late termination

The procedure for terminating a pregnancy at over 14 weeks involves inducing labour by introducing hormones (prostaglandin) into the womb. The labour may last for several hours and the procedure is much more upsetting for the woman than an early termination. Again, this type of termination does not affect the woman's ability to become pregnant again.

Other approaches

Prenatal diagnosis and the termination of pregnancy are controversial. Unfortunately, however, prevention cannot rely on the identification of carriers alone and screening cannot be effective and successful in the absence of prenatal diagnosis and pregnancy termination. Other methods of prevention are being developed, such as analysis of foetal cells in the mother's blood. This however has limitations and cannot offer to-date a reliable alternative to classical prenatal testing. Another technique is pre-implantation genetic diagnosis (PGD), which involves the use of DNA technology to analyse a few cells taken from the very early embryo or to select a healthy egg from a woman carrier to be fertilized in the laboratory and then introduced into the womb. PGD may prove more acceptable to those populations opposed to the termination of pregnancy, and may thus become more widely used once the technique becomes less costly and less technologically demanding.

How is β-thalassaemia major diagnosed?

A child born with β-thalassaemia major will show no visible signs of the disease. Even laboratory tests may fail to diagnose thalassaemia, particularly if the parents have not been tested, no prenatal tests were carried out, and there is no other affected child in the family. The reason thalassaemia is so hard to diagnose at this early stage is that the presence of sufficient amounts of foetal haemoglobin (HbF) ensures a balance in the number of globin chains – α and γ – that make up HbF, protecting the young child from the ineffective process of red blood cell production described earlier.

It is possible to diagnose β-thalassaemia major at this very early age by means of molecular techniques that identify mutations the child has inherited from each parent. However, this test is only likely to be carried out where a specific suspicion arises – for example, where parents discover that they are carriers only baby is born. Unfortunately, even where newborn screening programmes are well established, the diagnostic tests involved in identifying thalassaemia major are inconclusive at such an early stage. However, screening at this stage can be of use in diagnosing the presence of a variant such as HbE or HbS.

In most cases, thalassaemia major can be diagnosed before the age of 2 years. Thalassaemia intermedia, which in the majority of cases is a “milder” condition than thalassaemia major can however remain undiagnosed for longer periods. The table below shows the results of work done by some investigators on this matter.

Age at presentation of infants with thalassaemia major (TM) or thalassaemia intermedia (TI) (from Modell and Berdoukas 1984)

Age (years)	TM	TI
<1	75–62%	4–11%
1-2	35–29%	11–30%
>2	11–9%	22–59%

Haematological methods commonly used to diagnose thalassaemia major

(i.) Haematological indices. These haematological parameters are measured by electronic equipment – a red cell counter – used to assess the size and volume of red blood cells and the amount of haemoglobin contained in them. Thalassaemia is diagnosed where the size and volume of red blood cells and the concentration of haemoglobin inside them are significantly reduced, with haemoglobin levels of between 2–6g/dl. Some haematological indices most commonly found in patients with thalassaemia are shown below:

	mean	range
Hb g/dl	6.8	3.9–9.3
MCH pg	20.9	15–26
MCV FL	65.8	57–75
MCHC g/dl	30.9	26–34

The number of white blood cells may appear raised due to the presence of a large number of immature (nucleated) red blood cells, which the cell counter may mistakenly identify as white blood cells. However, this miscounting is easily clarified by further laboratory investigations.

(ii.) Blood film and RBC morphology. Observed under a microscope, the red blood cells appear paler (hypochromic) and smaller (microcytic) than normal and – very importantly – the majority have abnormal shapes: anisocytosis, poikilocytosis.

(iii.) Haemoglobin electrophoresis. This is a process that separates the different proteins that make up a haemoglobin molecule, i.e. HbA, HbA2 and HbF. A diagnosis of thalassaemia is indicated where levels of foetal haemoglobin are higher than normal and may vary between 20-90%. HbA2, which usually accounts for up to 3% of normal adult haemoglobin, may be non-existent, reduced, normal or slightly elevated.

(iv.) Molecular methods. These are specialised ways of confirming or obtaining more specific information in a diagnosis, using DNA investigation to establish, for example, the mutations that cause a condition – information that, in addition to confirming a diagnosis, also provides an indication of the clinical severity of the disease.

An investigation of haematological parameters as well as of genetic mutations to the α, β and γ genes are essential steps, both in confirming a diagnosis of thalassaemia and in deciding treatment. Although the diagnosis of β-thalassaemia major is usually fairly straightforward, difficulties may arise, particularly in developing countries where the

prevalence of diseases such as malaria can complicate diagnosis. For example, malaria can cause anaemia and splenomegaly, and although the haematological laboratory findings are quite different, it may be necessary to treat the patient with anti-malarial drugs before reassessing the patient's condition and diagnosis.

Other conditions may also cause anaemia and splenomegaly as well as raised HbF levels and a differential diagnosis is necessary with additional clinical and laboratory tests. It is very important to confirm an accurate diagnosis of thalassaemia before treatment.

The major haemoglobin disorders in summary

α-globin chain disorders	β-globin chain disorders
α-thalassaemias	sickle cell disorders
HbH disease	sickle cell anaemia (HbSS)
α-thalassaemia hydrops foetalis	HbS/β-thalassaemia
(= Hb Bart's hydrops foetalis)	HbSC disease
	HbSD disease
α-chain variants	other rare sickling disorders
	β-thalassaemias
	β-thalassaemia major
	β-thalassaemia intermedia
	HbE/β-thalassaemia
	other rare thalassaemias

What is Thalassaemia Major?

Thalassaemia is an inherited genetic disorder of the blood; more specifically, it is a disorder that results from abnormalities in the synthesis of the haemoglobin molecule contained in red blood cells.

The precise defect that leads to β-thalassaemia major lies in the gene controlling the production of β-chains in the globin part of haemoglobin. This defect makes it impossible for the body to produce healthy haemoglobin (a process known as erythropoeisis from the Greek *erythra*, meaning red cells and *poeisis*, meaning production). Haemoglobin requires the presence of equal quantities of both α-and β-chains to function properly. Reduced or no production of β-chains means that an excess of α-chains results. These excess α-chains are toxic and prevent the development of normal red blood cells. So the defect of the β-gene in individuals with thalassaemia major prevents the body from producing a sufficient quantity and quality of red blood cells. As a result, the body does not receive enough oxygen, because the red blood cells cannot transport it.

What are the consequences of the genetic defect in thalassaemia?

The two major consequences of the genetic defect of thalassaemia are:

1. severe anaemia
2. expansion of the bone marrow. The latter is a blood forming tissue (marrow) in the bones which expands greatly in an attempt to produce more and more red cells to fight the anaemia.

The above consequences lead to:

- poor growth
- impaired physical activities
- facial and other bone deformities
- fragile bones
- enlargement of liver and spleen

What is Haemoglobin

Haemoglobin is a specialised type of compound molecule -a protein -found in red blood cells, the main function of which is to transport oxygen to wherever it is needed in the body. Each red blood cell contains 300 million molecules of haemoglobin. A molecule of haemoglobin has two parts:

(i.) Globin. A protein called globin, made up of four chains arranged in matching pairs. In adult haemoglobin, the majority of the chains are α and β, making the major adult haemoglobin HbA (α2β2). To a smaller extent δ and γ- chains are produced, matching with a chains to form α2δ2 and α2γ2 (foetal haemoglobin).

(ii.) Haem-iron. A ring structure synthesised in the cell's mitochondrion and cytosol. An iron molecule contained in the haem enables the transport of oxygen around the body. This is because iron easily binds with and loses oxygen, making it the perfect means of delivering oxygen to the tissues and cells.

Normal adults have 4g of iron in their body, 75% of which – about 3g – is used to synthesise haemoglobin.

What are Genes

Genes are the biological units of inheritance, the unique blueprints for an individual organism, providing all the biological information needed for controlling growth and development throughout its life. Genes are in every cell (building block) of the body. The key part of each gene is a chemical substance called DNA (Deoxyribonucleic acid). Taken together, an organism's total DNA is called the "human genome" and contains about 100,000 genes. There are a number of genes that, when affected (i.e. damaged) cause different diseases. These are called genetic disorders. Thalassaemia major is a genetic disease because it results from a defect or damage to a gene – the gene that controls the production of β-chains – a very important part of normal adult haemoglobin molecules (α2β2). Thalassaemia major is passed on (inherited) from parents to children in a specific way called Mendelian autosomal recessive. It is "autosomal" because it involves a gene that is common to both males and females and "recessive" because the child must inherit a defective gene from the mother and the father to be affected. The child is not affected if only one defective gene is inherited from either the father or the mother.

What are Chromosomes

A great number of genes pined together in a long piece is called a chromosome. Each human cell (except sperm/egg cells) has two copies of each chromosome, one inherited from the mother and one inherited from the father. Humans have 23 pairs, 46 chromosomes in all. 22 pairs, 44 chromosomes are the same in both males and females called autosomes. One pair, the two chromosomes called the sex chromosomes, decide the gender.

Blood – the river of life

Blood is a vital fluid that brings nourishment to the body's organs and tissues and carries away waste substances. A healthy adult has about 5 to 6 litres of blood roughly 7–8% of total body weight. Blood is produced in the bone marrow, a tissue found in the middle (central cavity) of bones. In infants, blood cells are made in several body tissues. In adults, blood cells are only produced in the marrow of the skull, spine, ribs and pelvis.

Blood is moved around the body by the heart, which pumps blood through a network of "pipes" called blood vessels. There are three different types of blood vessels: arteries, veins and capillaries, each of a different size and function. Together, these vessels are known as the circulatory system.

Blood consists of plasma (the liquid part of blood), red blood cells (erythrocytes), white blood cells (leucocytes) and platelets (thrombocytes).

What is the role of Blood

Blood performs many important functions:

(i.) Transports oxygen: The body relies on blood to bring it the essential nutrients it needs to function, and to carry away the poisonous waste products it needs to get rid of. For example, all cells and living organisms need oxygen – a gas found in the air we breathe – to survive and function. The blood picks up oxygen from the lungs carrying it to different parts of the body.

(ii.) Picks up carbon dioxide, another gas that is a waste product formed by cells, carrying it back to the lungs to be released into the outside air. The blood also collects other waste products, such as urea and uric acid, carrying them to the kidneys and liver. Eventually, waste products are removed from the blood in urine and stools.

(iii.) The blood also transports special chemicals called hormones, which regulate the function of important systems of the body, such as the sexual and reproductive systems.

(iv.) Delivers nutrients to different parts of the body – proteins, fats and carbohydrates, produced from food broken down by the digestive system.

(v.) Helps the body fight infection and disease through cells that form part of its defence system, the immune system.

Whole blood

Whole blood is made up of two parts: non-cellular – the part that contains no cells – and cellular – the part that contains cells.

Our bodies are made up of trillions of microscopic units – tiny building blocks called cells. Cells are far too small to be seen by the naked eye. In most tissues, they are stuck together. But in blood, cells float around in the non-cellular fluid. Each cell has three major parts or compartments: the centre or nucleus, the substance around the nucleus known as the cytoplasm, and the structure surrounding the cell – the cell membrane. Numerous other smaller structures are found within each of these major cell compartments, each with a specific function. However, a large part of every cell is water, along with proteins, fats, carbohydrates, nucleic acids, dissolved molecules and inorganic ions. Proteins are the 'workhorses' of our cells, and there are 100,000 different types of proteins in our body. Some of the functions of proteins in cells include:

- providing the building blocks for most cellular structures
- acting as enzymes – catalysts for the chemical reactions that make life possible
- controlling communications between cell surfaces
- controlling the expression of genes
- replicating genetic material

The non-cellular part of blood is a yellowish liquid called plasma. The cellular part of blood is made up of three different types of cells: red blood cells or erythrocytes, white blood cells or leukocytes, and platelets or thrombocytes.

What is Plasma

Plasma makes up 55% of whole blood. It is made up of water and salts, as well as important proteins that it carries around the body, such as

- albumin – the main protein in blood
- globulins, including gamma globulin, which is composed of tens of thousands of antibodies that help the body fight infections and diseases
- fibrinogen, which helps the blood to clot, limiting the flow of blood out of the body after an injury

What are red blood cells (RBCs)

Red blood cells or erythrocytes (RBCs) make up about 45% of the total volume of blood. The body contains around 4,500,000-5,000,000 RBCs/cmm of plasma. RBCs also have the longest average lifespan of any of the cellular elements of blood – 100120 days. The main constituent of red blood cells (RBCs) is a protein called Haemoglobin.

The primary function of RBCs is to carry oxygen from the lungs around the body, binding the oxygen to haemoglobin, which it then delivers it to each tissue and cell to keep them healthy and functioning. Red blood cells contain many molecules of haemoglobin – as many as 300 million -which give the blood its red colour. In fact, RBCs are so packed with haemoglobin that they do not contain some of the parts found in other cells, such as a nucleus.

The membrane or outer layer of a red blood cell is very flexible, like a soap bubble. This allows the cell to bend in many directions without breaking, particularly when it passes through the tiniest blood vessels (the capillaries) to deliver oxygen wherever it is needed. RBCs also contain substantial amounts of an enzyme known as carbonic anhydrase, which plays an important part in transporting carbon dioxide from the tissues to the lungs.

What are white blood cells

White blood cells or leucocytes make up just 1% of blood. They play a vital role, working as the body's first line of defence against invading infectious agents such as bacteria, viruses, fungi and parasites. White blood cells are a diverse group of cell types, each contributing in a different way to fighting and preventing infection and tissue damage. They are usually classified according to their morphological characteristics:

- Granulocytes or polymorphonuclear cells, so called because of their granular appearance and lobed nuclei. These are subdivided according to the colour they assume upon staining in the laboratory:
    - neutrophils (72% of white cells), which are blue on staining
    - eosinophils (1.5% of white cells), which are red on staining
    - basophils (0.5% of white cells), which are purple on staining

- Other white cells are:
    - monocytes (4% of white cells)
    - lymphocytes (24% of white cells)

White blood cells are bigger than red blood cells but they are much fewer in number – about 7,000 in one cubic millimetre of blood – and their lifespan is much shorter, just 18–36 hours.

What are Platelets

Platelets play a single, crucial role in the blood-they begin the process of coagulation (forming the blood into a clot) to prevent the body from losing blood through a damaged blood vessel. Platelets are the smallest blood cells in the body. There are around 200,000 platelets in one cubic millimetre of blood, with a lifespan of 97–100 days. Both white blood cells and platelets (but not red blood cells) contain a central part called the nucleus and an outer margin called the cytoplasm.

The three types of blood cells all develop from the same starter (or precursor) cell, known as a haemopoietic stem cell. Starter cells multiply extremely quickly. In just four weeks, 10 starter cells can multiply to make 30 trillion red blood cells, 30 billion white blood cells and 1.2 trillion platelets – enough to replace every blood cell in the body.

What is the treatment of β-thalassaemia Major?

Over the last three decades, clinical observations and research have established that thalassaemia major is a treatable condition. Studies have shown that regular transfusion therapy with safe and appropriately processed blood, combined with regular and effective iron chelation tremendously increase patients' survival and quality of life.

This recommended treatment regime is focused on fighting the anaemia prevalent in thalassaemia and all its consequences, and on preventing progressive tissue iron-loading that may result from the disease itself and from the blood transfusion therapy used to treat the anaemia.

Blood Transfusion Therapy

Regular blood transfusions greatly contribute to the quality and length of life of patients with thalassaemia major, and have been a central aspect of the treatment of thalassaemia since the 1960s. If not effectively managed, the severe anaemia and over-expansion of the bone marrow characteristic of thalassaemia major can lead to:

- poor growth
- facial and other bone deformities
- fragile bones and bone fractures
- enlarged liver and spleen (organomegaly)
- impairment of normal physical activities

Regular blood transfusions on a life-long basis – at least until a cure for thalassaemia major becomes available – can counteract or even prevent the development of these symptoms. However, several factors must be taken into account when beginning blood transfusion therapy.

When to begin transfusion therapy

Transfusion therapy should only begin once a diagnosis of thalassaemia major is confirmed. As mentioned earlier, a confirmed diagnosis of thalassaemia major is based on:

1. laboratory tests (e.g. haematological, molecular or haemoglobin electrophoresis and other laboratory tests, such as high pressure liquid chromatography, (or HPLC)
2. genetic analysis to identify the nature of α- and β-thalassaemia mutations, as well as the presence of the Xmn1 restriction enzyme site – an indicator that can help predict the severity of the disease and identify the treatment regime most appropriate to each patient.

The severity of anaemia is usually assessed on the basis of levels of haemoglobin (Hb) in the blood. This is measured in grams per decilitre ($1/100^{th}$ of a litre) of blood. Haemoglobin is easily measured in a laboratory, usually using a machine called a cell counter. Older methods such as the Sahli technique can also reliably measure haemoglobin. A normal Hb level is generally considered to be between 13–16g/dl in men and 11–14g/dl in women and children. In both men and women, haemoglobin levels of between 8–11g/dl represent moderate anaemia, with severe anaemia at levels less than 8g/dl.

Patients should only begin transfusion therapy once thalassaemia has been confirmed through laboratory diagnosis and molecular studies (as described above), and when:

- Hb levels are registered at less than 7g/dl on two successive occasions, more than two weeks apart. Very occasionally, patients may thrive and grow normally with Hb values between 6-7g/dl but a decision not to transfuse under these circumstances requires great clinical experience and careful observation.
- Hb levels are >7g/dl but accompanying physical characteristics are noted, such as:
    - facial changes
    - poor growth and limited weight gain
    - bone fractures
    - extra-medullar hematopoiesis, resulting in tumour masses

Where these criteria are observed, transfusion therapy should not be delayed.

For more detailed information on aspects related to the treatment of complications please refer to TIF's publication *About Thalassaemia*.