HAEMOGLOBIN DISORDERS (HAEMOGLOBINOPATHIES)

BETA (β) THALASSAEMIA
ALPHA (α) THALASSAEMIA
SICKLE CELL DISORDERS

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FOREWORD BY THE PRESIDENT

This book contains basic information about β-thalassaemia, α-thalassaemia and sickle cell disease. Whether you are a carrier or a patient, or simply interested in finding out more about β-thalassaemia, α-thalassaemia and sickle cell disease, we encourage you to read this book. Every effort has been made by the authors to include all important information regarding the diseases, their inheritance, prevention and treatment.

If you need to know more or more details on any aspect described in this book, we advise you to consult your physician, genetic counsellor or national health authority. The authors of this book will also be very happy to answer your questions as far as possible.

I hope that this book, which constitutes part of our educational material, will contribute significantly to TIF’s efforts in spreading awareness across the world about haemoglobin disorders.

TIF is greatly indebted to the authors, Dr. Androulla Eleftheriou and Dr. Michael Angastiniotis, both of whom are members of TIF’s Scientific Advisory Panel, for their invaluable contribution to the preparation of this educational book containing Sections One (about β-thalassaemia), Two (about α-thalassaemia), and Three (about sickle cell disorders - SCD), all of which aim to provide basic information about haemoglobin disorders in a simple manner to the community at large.

PANOS ENGLEZOS
PRESIDENT, TIF
ABOUT THALASSAEMIA INTERNATIONAL FEDERATION

The Thalassaemia International Federation (TIF) was established in 1987 with the mission to support the establishment and promotion of national control programmes for the effective prevention and appropriate clinical management of haemoglobin disorders including thalassaemia and sickle cell disease in every affected country of the world. TIF is today an “umbrella” Federation, comprised of 91 national thalassaemia associations from 46 countries, embracing hundreds of thousands of patients worldwide.

TIF works in official relations with the World Health Organization (WHO) since 1996. It collaborates closely with scientific and medical professionals from more than 70 countries, with the most relevant international and European health bodies, pharmaceutical companies and agencies, and very importantly with other disease-orientated patients’ organizations: a network of collaboration that contributes immensely to the achievement of TIF’s mission and vision.

TIF’s educational programme is one of its most important and successful activities. It includes the organisation of local, national, regional and international workshops, conferences and seminars, as well as the preparation, publication and translation of leaflets, magazines and books for health professionals, patients/parents and the community at large, distributed to more than 60 countries in the world.

OUR MOTTO

“UNITY IS OUR STRENGTH”

OUR MISSION

“EQUAL ACCESS TO QUALITY HEALTH CARE FOR EVERY PATIENT WITH THALASSAEMIA ACROSS THE WORLD”
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GENERAL INTRODUCTION

INTRODUCTION
Haemoglobin disorders or haemoglobinopathies are a group of conditions affecting human blood —more specifically an important substance or protein called haemoglobin contained in the red blood cells, hence the name haemoglobin disorders or haemoglobinopathies. These proteins constitute an important part of the human blood, which is the vital fluid that brings nourishment, such as oxygen [O2], hormones, proteins, fats and carbohydrates, to the body’s organs and tissues, and carries away waste substances such as carbon dioxide [CO2], urea and uric acid.

BLOOD
In adults, blood is exclusively produced in a special tissue called marrow, which is found in the central cavity of the bones (bone marrow). Blood consists of two major components:

i. the plasma, which is the yellow liquid that constitutes about 55% of the volume of blood and contains water, salts and important proteins, and;

ii. three types of cells which are microscopic building blocks, trillions of which make up the human body. The cells found in blood are:
   • The white cells or leucocytes
   • The platelets or thrombocytes, and
   • The red cells or erythrocytes

Each type of blood cell has specific functions and each contributes, in its own special way, to the well-being of the human organism, including protection against infection (white cells); limiting blood loss when a vessel is damaged (platelets); and provision of oxygen to tissues and vital organs (red cells).

Many diseases in humans are caused by abnormalities in the blood and these are categorized according to the component of the blood which is affected: white cell diseases, platelet diseases and red cell diseases.

Red cell diseases include amongst others the haemoglobinopathies or haemoglobin disorders, the most severe of which are alpha [α-] and beta [β-] thalassaemia and sickle cell disease.

HAEMOGLOBIN
Each cubic millimetre of human blood contains 4,500,000 – 5,000,000 red cells and each one of them is packed with 300 million molecules of haemoglobin -the substance that gives blood its red colour (because of a particular substance or metal it contains), and most importantly its oxygen carrying capacity (oxygen being essential for the growth and performance of the cells and organs.
of the human organism). The haemoglobin molecule itself consists of two major parts: (i) the globin and (ii) the haem:

### Globin

Globin is a protein made up of smaller units, referred to as chains – the alpha (α) and the non-alpha such as beta (β), gamma (γ), and delta (δ) chains. The alpha (α) chains couple with equal amounts of beta (β) chains to make up the haemoglobin A (HbA), which is the main type of haemoglobin in adults and up to 10% of the haemoglobin of the foetus. Alpha chains also couple with other chains, making up the haemoglobins found at various stages of human life, from conception, through foetal life, to birth and after birth.

The ‘haem’ part of the haemoglobin molecule contains iron – the metal that is essential for the growth and normal functioning of the cells and that gives blood its red colour. Iron has the capacity to easily bind and lose oxygen, providing the haemoglobin molecule with the capacity to carry and distribute oxygen to tissues and organs of the body. Adults have about 4g of iron in their body, 75% of which is used to synthesize the haemoglobin molecules of the red cells.

The level of haemoglobin found in a routine laboratory blood examination will, therefore, reflect the level of the individual’s iron.

### INHERITANCE

Haemoglobinopathies are genetic or hereditary disorders that are passed on from parents to children according to a specific pattern of inheritance known as “Mendelian recessive autosomal pattern of inheritance”. They are called genetic because all characteristics are passed on from

**NOTE:** The words alpha, beta, gamma and delta, where met in this text will be referred to with their respective abbreviations α, β, γ, δ.
parents to children through genes, which are the biological units of inheritance that provide all the information needed for controlling growth and development throughout human life. In the case of haemoglobinopathies, the contribution of genes is necessary from both parents (recessive inheritance) for the inheritance of these disorders, which can affect male and female children alike (autosomal).

**Deoxyribonucleic Acid** is a chemical substance often referred to by its abbreviation, DNA, which constitutes the key component of genes, of which a great number are needed to carry out the many and complex biological functions of the human organism. Genes are linked together in the cell on long piles of DNA called chromosomes, of which there are 23 pairs, half inherited from one and half from the other parent.

In the case of adult haemoglobin, the production and synthesis of its α- and β-chains, which constitute its major component, is controlled by genes on specific chromosomes. Four α-genes on chromosome 16 and two non-α-genes, such as (β, γ and δ) on chromosome 11, are responsible for the production, in exactly equal numbers, of α- and β- chains, respectively.

The individuals who have a defect in one of the α-genes responsible for the production of α-chains, which may cause reduced production of these chains, are called α-thalassaemia carriers. If the defect involves more of the α-genes, then fewer α-chains are produced and the individual may be affected more significantly.

Similarly, a defect in the gene responsible for the production of β-chains may cause a small or a severe reduction of β-chains.

The degree of β-chain reduction will determine whether an individual is only a β-thalassaemia carrier, or a patient with β-thalassaemia intermedia or major.

In contrast to the thalassaemias, in which the defect in the genes results in reduced production of α- and β- chains (α or β), there are conditions in which the defect in the genes results in the production of “wrong” kinds of proteins whose structure, as well as their function, are different from that
of the adult common haemoglobin, (HbA). These are called abnormal or structural haemoglobin variants. Reference is made to the inheritance and clinical outcome of these in all three sections (1, 2 and 3), accordingly.

**THE MAJOR HEAMOGLOBIN DISORDERS ARE:**

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<th>α-chain disorders</th>
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**β-thalassaemias**

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<td>HbE/β-thalassaemia</td>
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<td>Other rare thalassaemias</td>
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This book provides information on β- thalassaemia, α-thalassaemia and the variant haemoglobin S (HbS), in this order in sections One, Two and Three.
ABOUT
BETA \((\beta)\)
THALASSAEMIA

SECTION 1
HAEMOGLOBIN DISORDERS (HAEMOGLOBINOPATHIES)

BETA (β)-THALASSAEMIA (THALASSAEMIA) OR MEDITERRANEAN ANAEMIA (ANAEMIA) OR COOLEY’S ANAEMIA (ANAEMIA)

INHERITANCE PATTERNS OF β-THALASSAEMIA

Pattern A
Both parents with functional β-genes: when in both parents the β-genes are unaffected, i.e. fully functional, all their children will inherit two unaffected, functional β-globin genes, and all children will thus have common adult haemoglobin (HbA).

Pattern B
When one of the parents carries an affected β-gene, i.e., when he/she is a β-thalassaemia carrier and the other parent carries a functional β-gene, then each child born to these parents (i.e. at every pregnancy) has a one-in-two (50%) chance of inheriting the affected β-globin gene from the carrier parent. (Fig. 01)

One may also come across other names describing a carrier of β-thalassaemia, such as:
• Carrier of the β-thalassaemia trait
• Individual heterozygous for β-thalassaemia
• Individual with β-thalassaemia minor
In addition, β-thalassaemia may be referred to as Cooley’s anaemia.

ABOUT CARRIERS OF β-THALASSAEMIA

A carrier is a person who has a fully functional gene on one chromosome and a defective β-gene on the other. Carriers of β-thalassaemia do not have a disease. They have no physical or mental symptoms and do not require a special diet, medical advice or treatment. Carrying β-thalassaemia has no effect on health, length or quality of life.

Carriers do have smaller red blood cells than non-carrier individuals. This is because a carrier has inherited an affected β-gene from one parent, which, as a result, makes less human adult haemoglobin (HbA). His/her red cells thus contain less haemoglobin than usual and consequently their size is smaller and their colour paler than non-carriers’ cells. Carriers, however, make up for this by producing more red cells, and in this way the blood continues to function and serve the human organism normally.

The carrier status cannot become a disease over time. Indeed, most individuals will be unaware that they are carriers unless they are specifically tested. Some carriers may experience mild anaemia, which can be inaccurately diagnosed as iron deficiency anaemia. Laboratory tests, however, can differentiate between the two and physicians may then advise the individuals or carriers accordingly.
ONE PARENT IS A CARRIER OF β-THALASSAEMIA AND THE OTHER HAS UNAFFECTED β-GLOBIN GENES

FOR EVERY PREGNANCY THE CHANCES ARE:

50% UNAFFECTED

50% CARRIERS OF β-THALASSAEMIA
Frequently asked questions about carriers

- **What about pregnant women who are carriers?**
  Like other pregnant women, those who carry β-thalassaemia can also become iron deficient and may need extra iron. The mild anaemia due to carrying β-thalassaemia can, however, become more severe during pregnancy and a pregnant carrier may, though very rarely, need a blood transfusion. The anaemia will improve after the baby is born.

- **Is there any treatment or intervention to stop being a carrier?**
  A person who is born carrying B-thalassaemia will always carry it in his/her genes throughout life.

- **Can the B-thalassaemia carrier status be transmitted or acquired at a later stage in life?**
  The B-thalassaemia carrier status cannot be acquired or transmitted through the environment, transfusion or other means by which people become infected. Carriers who have inherited B-thalassaemia from their parents could pass it on to their children.

- **Can carriers donate blood?**
  Carriers may be suitable blood donors if their haemoglobin level meets the national inclusion criteria for donating blood.

- **What should carriers do if they are thinking of having children?**
  Carriers should encourage their partners to have a special blood test which ideally should be done before they start a pregnancy. In this case, partners who are both carriers should see a genetic counsellor or a physician to obtain further information and take the time to consider and decide what is best for them.

- **Is there anything else that a carrier should do?**
  A carrier should let their brother or sister know about their condition and advise them to also have a blood test for Hb disorders.

**Pattern C**

Partners who both carry an affected β-gene are referred to as an “at-risk” couple. As stated above, although being a carrier of B-thalassaemia has no adverse health effects, if he/she plans to make a family with another carrier, then at each and every pregnancy, the risks involved are as follows:

- **i.** a one-in-four (25%) chance that the child will have B-thalassaemia major/intermedia, the full-blown disease. B-thalassaemia intermedia/major is also known as Mediterranean Anaemia or Cooley’s Anaemia and the patient may also be referred to as homozygous for B-thalassaemia,

- **ii.** a one-in-two (50%) chance that the child will be a carrier of B-thalassaemia, and

- **iii.** a one-in-four (25%) chance that the child will have completely unaffected, fully functional B-genes.

[FIG 02]
UNAFFECTED GENES

β-THALASSAEMIA

FIG. 02

BOTH PARENTS ARE CARRIERS OF β-THALASSAEMIA

FOR EVERY PREGNANCY THE CHANCES ARE:

- -  
25% WITH β-THALASSAEMIA MAJOR

β -  
50% CARRIERS OF β-THALASSAEMIA

- β  
25% UNAFFECTED

β β
δβ-thalassaemia
In this form of thalassaemia, both the δ-genes and the β-genes are not functioning, a situation partly balanced by increased production of other chains, such as the γ-chains, since the γ-gene is fully functional.

Like the β-thalassaemia carrier, the δβ-thalassaemia carrier is a healthy individual and needs no medical treatment, but the affected gene can be passed on from the parent to his/her children. A child inheriting either one δβ-gene from each δβ-carrier parent or one δβ-gene from one parent and one β-gene from the other parent will develop a severe haemoglobin disorder, similar in its clinical outcome to β-thalassaemia major or β-thalassaemia intermedia, and will thus require similar clinical management.

“Abnormal Haemoglobins”
A number of “abnormal” types of adult haemoglobin have been identified, which differ both in their structure and clinical outcome. These are also known as “structural haemoglobin variants” and include HbS, which is the haemoglobin responsible for sickle cell disease (SCD), haemoglobin E (HbE), haemoglobin C (HbC), haemoglobin D (HbD) and haemoglobin Lepore (Hb Lepore). These are passed on from parents to their children and are inherited in exactly the same way as β-thalassaemia. However, only those individuals that inherit from both parents Hb Lepore or HbS will develop clinically significant conditions that require medical care.

Inheritance of the other abnormal haemoglobins, i.e. HbC, or HbD or HbE from both parents is not related to any significant clinical outcome, and so these do not require any medical attention.

However, inheritance of an “abnormal” haemoglobin, Lepore, E or S from one parent and β-thalassaemia from the other parent results in compound haemoglobinopathies, such as Hb Lepore/β, HbE/β, and HbS/β, which are clinically significant blood disorders similar to β-thalassaemia major/intermedia and require appropriate medical care. More details associated with the most common of the “abnormal” haemoglobin, HbE, are provided below.

Haemoglobin E (HbE)
HbE is one of the most common abnormal haemoglobin variants, particularly prevalent amongst people of South East Asian origin. Like the β-thalassaemia carrier, the HbE carrier is a healthy individual and needs no medical treatment. However, the affected genes can be passed on from the parent to his/her children according to the inheritance pattern described earlier for β-thalassaemia. A child inheriting two HbE genes, one from each of his/her parents, will still be healthy and not require medical care.

HbE becomes important only when the child inherits from one parent the β-thalassaemia gene and from the other parent the HbE gene. This will result in HbE/β-thalassaemia which is a serious disorder, the clinical symptoms of which are similar to those seen in β-thalassaemia intermedia, but which may sometimes be as severe as those seen in thalassaemia major. (FIG 03)
ONE PARENT IS A CARRIER OF HbE AND THE OTHER OF β-THALASSAEMIA

FOR EVERY PREGNANCY THE CHANCES ARE:

25% WITH HbE/β-THALASSAEMIA
25% CARRIERS OF HbE
25% CARRIERS OF β-THALASSAEMIA
25% UNAFFECTED
Sickle cell disorders are different in cause and clinical outcome from β- and α-thalassaemia, and these are described in detail in section 3. Inheritance of the β-thalassaemia gene from one parent and the HbS gene from the other will result in a haemoglobin disorder called HbS/β-thalassaemia. The clinical outcome of this compound haemoglobin disorder is similar to sickle cell disease, which is very different from β-thalassaemia major/intermedia and which consequently is different in its clinical management (see section 3 for more detailed information).

HOW DOES ONE KNOW WHETHER ONE IS A β-THALASSAEMIA CARRIER?
In most cases, simple but specific laboratory tests can identify whether a person is a carrier of β-thalassaemia or any other haemoglobin disorder.

LABORATORY TESTING TO ESTABLISH WHETHER ONE IS A CARRIER OF β-THALASSAEMIA
Laboratory testing for thalassaemia includes a routine blood test known as a Complete Blood Count (CBC), which involves measuring the content of haemoglobin inside the red cells, and other parameters such as the Mean Corpuscular Volume (MCV) and the Mean Corpuscular Haemoglobin (MCH), both of which will be lower in carriers of β-thalassaemia.

Red blood cells are also seen under a microscope in order to examine their size and shape. The red cells of a thalassaemia carrier will be a paler shade of red (hypochromic), of various shapes (poikilocytosis), and smaller (microcytosis) compared to the red blood cells of a non-carrier, which are a darker red in colour, round and concave in shape.

Another test that is used to determine the presence of β-thalassaemia includes a laboratory process known as haemoglobin electrophoresis, which enables measurement of the quantity of the major HbA and minor HbA2 components of adult haemoglobin, of which the latter (i.e. HbA2) is always raised in the carrier. Other haemoglobins present in adult red cells, such as foetal haemoglobin, HbF, and HbS, may also be measured by electrophoresis. In most cases, the above tests are sufficient to determine whether an individual is a carrier of β-thalassaemia.

Other ways to diagnose thalassaemia include iso-electric focusing (IEF), which is another kind of electrophoresis, and High Pressure Liquid Chromatography (HPLC for short) and Capillary Electrophoresis, which are considered today, as methods of reference both for screening and for confirming the diagnosis of haemoglobin disorders.

Where the above tests are inconclusive and do not allow the laboratory scientists to provide a confirmed diagnosis, other more specialised tests are available, such as genetic tests, i.e. tests that are based on the examination of the individual’s DNA. For this test, blood is often required from other members of the family for a definite diagnosis to be made.

On occasions where iron deficiency exists, it may obscure the diagnosis and so it must be excluded as the cause of the red cell abnormalities. It may be necessary to correct the iron deficiency first by giving iron tablets to the individual and repeating the test in at least one month’s time, after which the diagnosis may be confirmed.
The choices available to an ‘at risk couple’
Today, partners in a relationship who are aware that they are carriers of β-thalassaemia have a number of choices with regard to having a family. These should be discussed as early as possible with an expert health professional, a genetic counsellor if available.

IF A COUPLE DECIDES TO PROCEED WITH PREGNANCY AND TEST THE FOETUS
There are three methods of prenatal diagnosis that can determine whether a foetus has β-thalassaemia major or intermedia:

i. Amniocentesis
This test is performed in the second trimester of pregnancy, after about 15 weeks’ gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother’s abdomen. A small amount of amniotic fluid, containing cells from the foetus, is withdrawn. This is then analysed in the laboratory to determine whether the foetus has b-thalassaemia (major or intermedia). The specialist obstetrician will be able to explain and discuss in detail all aspects of this procedure, including potential risks for the couple involved.

ii. Cordocentesis
This is a test performed after 18 weeks of pregnancy. Under ultrasound guidance, a fine needle is inserted through the abdomen into the foetal umbilical cord, through which a small volume of blood from the foetus is aspirated. The blood is analysed in the laboratory. The specialist obstetrician will be best able to explain and discuss with you causes of failure in obtaining pure foetal blood, as well as any other potential risks when undergoing the procedure. Early and specific diagnosis with molecular methods has almost completely replaced cordocentesis, which is now mainly indicated in pregnant women who report late, when CVS is inconclusive.

iii. Chorionic Villus Sampling (CVS)
This is another method of diagnosing haemoglobin disorders in the foetus and can be performed earlier than both amniocentesis and cordocentesis, at about 10-11 weeks’ gestation. Using ultrasound as a guide, the specialist obstetrician removes a small sample of cells from the chorionic villi, i.e. cells that contain the same genetic information as the foetus and which will eventually form the placenta. The cells are removed either with 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 other prenatal diagnosis methods, information on potential risks and benefits of using this procedure is provided to the couple by the specialist obstetrician.
How is the diagnosis of the foetus made after obtaining samples using the above methods of prenatal tests?

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

These tests confirm whether the foetus is healthy, a carrier or affected. The couple may decide to either proceed with the pregnancy, accepting that lifelong treatment will be necessary, or to end the pregnancy, if this is possible. If pregnancy termination is the choice, the specialist obstetrician will explain how this is done, depending on the stage of the pregnancy.

Other approaches

Prenatal diagnosis and the termination of pregnancy are methods that may not be acceptable to every couple at risk due to religious, cultural or personal beliefs.

Prevention cannot rely on the identification of carriers alone. If prenatal diagnosis and pregnancy termination are not acceptable, other methods of prevention that minimise intervention and psychological stress have been developed, while others are still in the research stage. For example, pre-implantation genetic diagnosis (PGD) is a refined, established laboratory procedure whereby:

i. cells from a very early embryo (resulting from in-vitro fertilisation) are analysed in the laboratory to confirm the presence or absence of a haemoglobin disorder. Unaffected embryos are then selected for implantation into the womb of the carrier woman;

ii. unfertilised ova (eggs) which do not carry a haemoglobin disorder or mutation, detected by polar body diagnosis, are selected from the carrier woman and then fertilised using her husband’s sperm. The selected fertilised ova are then introduced into her womb.

PGD is, however, a costly and technologically demanding procedure and several attempts are often necessary for a successful pregnancy.

β-THALASSAEMIA (MAJOR OR INTERMEDIA, OTHERWISE KNOWN AS MEDITERRANEAN ANAEMIA OR COOLEY’S ANAEMIA)

Patients with β-thalassaemia major, the most severe form of thalassaemia, cannot make adult haemoglobin, and as a consequence cannot produce normal red blood cells. In these individuals, each red blood cell contains much less haemoglobin, and there are far fewer red cells than the normal range. This causes anaemia, which is severe in these patients.

A child with β-thalassaemia major does not, however, develop severe anaemia until three months to one year of age. If left untreated, affected children have a very poor quality of life and most will die at a very young age. The patients who have β-thalassaemia intermedia, which is considered in the majority of cases to be a “milder” condition than β-thalassaemia major, can manage without regular blood transfusions, at least in the early years of life, although they still have a serious anaemia. Nevertheless, the anaemia may get worse with age, and they may need to start regular blood transfusions later in childhood or in adult life. Many other medical complications, including endo-
crine, cardiac and hepatic, are seen in both β-thalassaemia major and intermedia. Because of this, multidisciplinary medical care is required.

**WHAT IS THE TREATMENT OF β-THALASSAEMIA MAJOR?**

The basic treatment is regular blood transfusion, usually every two to four weeks. Children who are transfused appropriately grow well and have a normal life. However, to live past their twenties, patients with β-thalassaemia major also need to start a specific treatment from early childhood to remove the excess iron, which is released from the haemoglobin of the transfused red cells, as these continuously break down. As a result, iron builds up in the body and causes overload, which can ultimately damage vital organs, such as the heart, liver and endocrine glands. Iron can be removed by specific drugs, called iron chelating agents, that have the capacity to bring it out in the urine and/or the stools. The traditional and first iron chelating agent to be used with efficiency and safely is Desferrioxamine, which is injected under the skin for many hours almost every day, using a small pump. Although difficult and cumbersome, this treatment has proved to be a life-saving one for decades.

The outlook is, however, steadily improving as new iron chelating agents that can be taken by mouth are increasingly becoming available. Already, two orally taken drugs, Deferiprone (L1) and Deferasirox, are available in many countries and are in use by many thousands of patients across the world.

Children born today with thalassaemia major or intermedia can be expected to live an almost normal length of life, provided that they can obtain all the appropriate treatment according to consensus guidelines.

Considerable research is focused on further improving medical care of thalassaemia major through pharmaceutical substances that may ultimately lead to a reduction in the need for blood transfusion therapy and iron chelation.

Cure of β-thalassaemia can only currently be achieved by haemopoietic stem cell transplantation (HSCT), which includes bone marrow transplantation (BMT). This has been shown to be successful in the majority of cases, provided that a fully matched (HLA compatible) sibling (brother or sister) can be identified, and the patient is in a very good condition clinically, i.e. he or she has been receiving appropriate clinical management from the early years. However, only a relatively small percentage of patients (about 20%) will have a fully matched donor, and considering that this procedure is still an expensive one, BMT cannot be the solution to the total cure of this disease for the majority of patients.
Pre-implantation Genetic Diagnosis (PGD-HLA)
One possible answer to the limitations associated with BMT, particularly with regard to finding a suitable donor, is for the parents to have another child who will be fully compatible with the living, affected one.

In order to ensure that this new child will be a compatible donor, a special process known as PGD-LA has been developed in recent years. According to this process, the embryo to be implanted into the woman’s womb is selected in the laboratory not only to be free from thalassaemia, as in the PGD technology described previously in the context of prevention, but also to have the same tissue characteristics (HLA type) as the living, affected child. In such a case, blood from the umbilical cord will be taken at birth, the cells of which may be used for transplanting into the patient. In other words, the “new” baby is selected from the beginning to be a perfect donor for his/her living affected brother or sister.

This is a laborious process, and not ethically approved by all. Nevertheless, it may provide a better chance of a matched donor for curing patients with β-thalassaemia major and other severe hereditary disorders.

Gene therapy
Another final cure for thalassaemia could be provided by means of another new and promising scientific process, called gene therapy. This is still experimental and it involves correcting the affected gene outside of the body, in the laboratory, and then replacing it into the patient’s blood-forming tissues, making them capable of producing new red cells, which will contain normal haemoglobin (HbA). The world thalassaemia medical community and patients/parents’ communities very much look forward to the success of this method which does not depend on donors as in the case of BMT, but, on the contrary, on the patient’s own cells. This procedure does not have the limitations encountered in bone marrow transplantation. It is hoped that science will soon overcome the many current technical difficulties and make the dream of a total cure a reality for all. A specialist physician or genetic counsellor or TIF will be able to provide more information and update you on all the above curative procedures.

HOW IS B-TALASSAEMIA MAJOR/INTERMEDIA DIAGNOSED?
A child newly born with β-thalassaemia major/intermedia will show no visible signs of the disease. Even laboratory tests may fail to diagnose thalassaemia, particularly if the parents have not been tested, if no prenatal tests were carried out, and if there is no other affected child in the family. Laboratory testing at this early stage will be of value in diagnosing the presence of “abnormal” haemoglobins, such as HbE or HbS.

In most cases, β-thalassaemia major can be diagnosed in the first few months and before the age of 2 years.

β-thalassaemia intermedia, which in the majority of cases is a “milder” clinical condition than β-thalassaemia major, can, however, remain undiagnosed for longer periods.
DIAGNOSING THALASSAEMIA MAJOR/INTERMEDIA IN THE LABORATORY

Haematological parameters
In thalassaemia major/intermedia, the size and volume of red blood cells and the concentration of haemoglobin inside them are significantly reduced. Haemoglobin levels are very low. Some haematological indices most commonly found in patients with thalassaemia (major) are shown below:

- Haemoglobin (Hb) g/dl 6.8 (range 3.9-9.3)
- Mean Corpuscular Haemoglobin (MCH) pg 20.9 (range 15-26)
- Mean Cell Volume (MCV) FL 65.8 (range 57-75)
- Mean Corpuscular Haemoglobin content (MCHC) g/dl 30.9 (range 26-34)

Morphology of RBC
Observed under a microscope, the red blood cells appear paler (hypochromic) and smaller (microcytic) than normal and, very importantly, the majority have abnormal sizes and shapes – anisocytosis and poikilocytosis respectively – changes which are more marked than those seen in the carrier.

Haemoglobin electrophoresis
This is a laboratory process that separates the different proteins that make up a haemoglobin molecule – HbA, HbA2, and HbF. A diagnosis of thalassaemia major/intermedia is indicated where:

- levels of foetal haemoglobin are higher than normal and may vary between 20-90%,
- HbA2, which usually contributes to up to 3% of normal adult haemoglobin, may be non-existent, reduced, slightly elevated, or even within normal range.

Molecular methods
These are laboratory methods used to confirm or obtain more specific information with regard to the diagnosis. They are based on DNA technology, which identifies the mutations (the genetic changes) that cause the disorder – information that, in addition to confirming a diagnosis, may also provide an indication of the clinical severity of the disease.

Although the laboratory and clinical diagnosis of β-thalassaemia major/intermedia is usually fairly straightforward, difficulties may arise, particularly in developing countries where the prevalence of other diseases such as malaria can complicate the diagnosis.

For example, malaria can cause anaemia and splenomegaly, and, although the haematological laboratory findings are quite different from those seen in thalassaemia major/intermedia, it may be necessary to treat the patient with anti-malarial drugs before reassessing his/her condition and diagnosis.

Other conditions may also cause anaemia and splenomegaly as well as raised HbF levels and additional clinical laboratory tests are necessary to differentiate and confirm the diagnosis of thalassaemia major/intermedia. An accurate diagnosis of thalassaemia is essential before the initiation of treatment.
CAN PATIENTS WITH THALASSAEMIA MAJOR/INTERMEDIA HAVE CHILDREN?

Yes, many adult patients are now married and have become parents or even grand-parents (in some countries). The possibilities of passing on their genes to their children are as follows:

i. Children from parents of whom one has β-thalassaemia major/intermedia and the other has fully functional β-genes will all be carriers of β-thalassaemia (in which case, they will be free of thalassaemia disease, and will not need any medical treatment or monitoring). (FIG. 04)

ii. Children from parents of whom one is a β-thalassaemia carrier and the other is a patient with β-thalassaemia major/intermedia will have a one-in-two chance (50%), to be carriers of β-thalassaemia (and be free of the disease) and a one-in-two (50%) chance to be patients with β-thalassaemia major/intermedia. (FIG. 05)

iii. When both parents are patients with β-thalassaemia major/intermedia, all children will also be patients with β-thalassaemia major/intermedia. (FIG.06)
FIG. 04

ONE PARENT WITH THALASSAEMIA MAJOR/INTERMEDIA AND THE OTHER WITH UNAFFECTED GENES

FOR EVERY PREGNANCY THE CHANCES ARE:

100% CARRIERS OF β-THALASSAEMIA
ONE PARENT WITH THALASSAEMIA MAJOR/INTERMEDIA AND THE OTHER A CARRIER

FOR EVERY PREGNANCY THE CHANCES ARE:

- 50% PATIENTS OF β-THALASSAEMIA
- 50% CARRIERS OF β-THALASSAEMIA
FIG. 06

BOTH PARENTS ARE PATIENTS WITH β-THALASSAEMIA MAJOR/INTERMEDIA

FOR EVERY PREGNANCY THE CHANCES ARE:

100% PATIENTS OF β-THALASSAEMIA MAJOR/INTERMEDIA
ABOUT

ALPHA (α)

THALASSAEMIA

SECTION 2
HAEMOGLOBIN DISORDERS (HAEMOGLOBINOPATHIES)

ALPHA (α)-THALASSAEMIA

INHERITANCE OF α-THALASSAEMIA
Figure 01 demonstrates the various types of alpha thalassaemia resulting from the possible combinations of functional and non-functional α-genes.

Silent carrier of α-thalassaemia or α+-thalassaemia carrier
The individual who has only one (out of the four) non-functional* α-gene is a silent carrier of α-thalassaemia, also referred to as an α+-thalassaemia carrier. The other three α-genes, which are fully functional, produce nearly normal amounts of haemoglobin. The defective α-gene may or may not result in slightly smaller red cells. For this reason, diagnosis by simple microscopic examination of the blood in the laboratory may be very difficult to be established, hence the term “silent” used to describe these carriers. Only very specific laboratory tests, based on DNA analysis, can accurately diagnose a silent carrier of α-thalassaemia (see below).

When one parent has all four α-genes functional and the other parent is a silent carrier of α-thalassaemia
In this case, at each pregnancy there is a one-in-two (50%) chance that the children will have all four of their α-genes functional and produce common haemoglobin (HbA) and one-in-two (50%) chance that the children will be silent carriers of α-thalassaemia, like their carrier parent.

Carrier of alpha zero (αo) thalassaemia
The individual who has two (out of four) α-genes missing or non functional is a carrier of alpha zero (αo) thalassaemia. These individuals may also be referred to as carriers of α-thalassaemia minor or carriers of α-thalassaemia trait. The two missing, or defective, α-genes may be on the same chromosome (cis position) or on different chromosomes (trans position) as shown in figure 01, types 3 and 4, respectively.

When both parents are silent carriers of α-thalassaemia.
At each pregnancy, there is a one-in-four (25%) chance that a child will have the common haemoglobin (HbA), a one-in-two (50%) chance that a child will be a silent carrier, and a one-in-four (25%) that a child will be a carrier of αo- thalassaemia. (FIG. 02)

ABOUT SILENT CARRIERS OF α-THALASSAEMIA AND CARRIERS OF ALPHA-ZERO THALASSAEMIA
Carriers of α-thalassaemia (silent and α-zero), like carriers of β-thalassaemia or sickle cell disease, do not have a disease. They have no physical or mental symptoms and do not require a special diet, medical advice or treatment. Therefore, carrying α-thalassaemia has no effect on health, length or quality of life.

The red blood cells are usually smaller, more so in the case of αo-thalassaemia, than those of non-carrier individuals, since the quantity of haemoglobin that they produce is reduced. When the red cells are examined under the microscope, apart from being smaller (microcytic), they may be paler (hypochromic) with unequal size (anisocytosis) and shape (poikilocytosis), compared to red cells of non-carriers.

*Functional: with normal capacity to produce α-chains / Non-Functional: lacking normal capacity to produce α-chains, defective
FOUR GENES FULLY FUNCTIONAL. THE INDIVIDUAL HAS COMMON ADULT HEMOGLOBIN (HbA)

ONE GENE IS NONFUNCTIONAL. THE INDIVIDUAL IS A SILENT CARRIER OF α-THALASSAEMIA (α⁺-THALASSAEMIA CARRIER)

TWO GENES ON DIFFERENT (trans) CHROMOSOMES NONFUNCTIONAL. THE INDIVIDUAL IS A CARRIER OF α⁰-THALASSAEMIA

TWO GENES ON THE SAME (cis) CHROMOSOME NONFUNCTIONAL. THE INDIVIDUAL IS ALSO A CARRIER OF α⁰ -THALASSAEMIA

THREE GENES ARE NONFUNCTIONAL. THE INDIVIDUAL HAS HbH DISEASE

ALL FOUR GENES NONFUNCTIONAL. THE INDIVIDUAL CANNOT SURVIVE AND WILL DIE BEFORE BIRTH AS HYDROPS FOETALIS

FIG. 01

ALPHA THALASSAEMIA TYPES RESULTING FROM POSSIBLE COMBINATIONS OF FUNCTIONAL AND NON FUNCTIONAL α-GENES
BOTH PARENTS ARE SILENT CARRIERS OF α-THALASSAEMIA (α⁺THALASSAEMIA)

FOR EVERY PREGNANCY THE CHANCES ARE:

- 25% UNAFFECTED
- 50% SILENT CARRIERS OF α-THALASSAEMIA (α⁺-THAL)
- 25% CARRIERS OF α°-THALASSAEMIA
The carrier status cannot become a disease over time. Indeed, most will be unaware that they are carriers, unless specifically tested. However, some carriers may experience mild anaemia, which can be inaccurately diagnosed as iron deficiency anaemia. Laboratory tests, however, can differentiate between the two states.

**Frequently asked questions about carriers (silent or αο-thalassaemia)**

- **What about pregnant women who are carriers?**
  Like other pregnant women, those who carry α-thalassaemia can become iron deficient and may need extra iron. The mild anaemia due to carrying α-thalassaemia can, however, become more severe during pregnancy. The anaemia will improve after the baby is born.

- **Is there any treatment or intervention to stop being a carrier?**
  No, a person who is born carrying α-thalassaemia will always carry it in his/her genes throughout life.

- **Can the α-thalassaemia carrier status be transmitted or acquired at a later stage in life?**
  The carrier status cannot be acquired or transmitted through the environment, transfusion or other means by which people become infected. Carriers inherit α-thalassaemia from their parents and could pass it on to their children.

- **Can carriers donate blood?**
  Carriers may be suitable blood donors if their haemoglobin level meets the national donor inclusion criteria.

- **What should carriers do if they are thinking of having children?**
  Carriers should encourage their partner to have a blood test specifically for haemoglobin disorders. This should ideally be done before they start a pregnancy. If their partner is also a carrier then they should both see a genetic counselor or a specialist physician to obtain further information.

- **Is there anything else that a carrier should do?**
  A carrier should let his/her brother(s) and/or sister(s) know about it and advise him/her/them to also have a blood test for Hb disorder.

**Combinations of α+ and αο-thalassaemias**

The various types of α-thalassaemia genes (α+ and αο), as described above, combine in different ways to produce blood disorders that range from mild to severe in their effect on the human body. They are inherited in exactly the same way as all haemoglobin disorders, according to the Mendelian pattern as described earlier in the general introduction (inheritance).

**Both parents carriers of αο-thalassaemia**

If both parents are carriers of αο-thalassaemia with a functional and a non-functional gene on each chromosome, i.e. the two nonfunctional α-genes are on different chromosomes (trans position), all their children will be carriers of αο-thalassaemia exactly as their parents. [FIG. 03]

**“At-risk couples”**

i. When both parents are carriers of αο-thalassaemia with two non-functional α-globin genes on the
FIG. 03

BOTH PARENTS ARE CARRIERS OF $\alpha^0$-THALASSAEMIA
THALASSAEMIA GENES ON DIFFERENT CHROMOSOMES (trans)

FOR EVERY PREGNANCY THE CHANCES ARE:

100% CARRIERS OF $\alpha^0$-THALASSAEMIA (trans)
same chromosome (cis position), the possibilities at each pregnancy are:

• one-in-four (25%) chance that a child will have fully functional α-genes, and will thus have common haemoglobin (HbA)
• one-in-two (50%) chance that a child will be carrier of α²-thalassaemia (cis type) and
• one-in-four (25%) chance to inherit α-thalassaemia major, (otherwise known as Hydrops Foetalis), in which all four α-genes are non-functional (see below for more details) (FIG. 04)

ii. When one parent is a carrier of α²-thalassaemia, i.e. with two non-functional α-genes on the same chromosome (cis position) and the other parent is a carrier of silent α-thalassaemia, i.e. has one defective α-gene on one chromosome, then this couple is also at-risk, and the possibilities in each pregnancy include:

• one-in-four (25%) chance that the child will be born with a clinically significant condition, Haemoglobin H disease (see below for more details), where 3 out of 4 α-genes are non-functional,
• one-in-four (25%) chance to be unaffected and have fully functional α-genes,
• one-in-four (25%) chance to be a silent carrier of α-thalassaemia and,
• one-in-four (25%) chance to be a carrier of α²-thalassaemia. (FIG. 05)

Individuals with HbH disease and inheritance patterns

i. HbH / carrier of silent α-thalassaemia

When one parent has HbH disease, and the other parent is a carrier of silent α-thalassaemia, then each child, at each pregnancy, has a

• one-in-four (25%) chance to be a carrier of silent α-thalassaemia,
• one-in-two (50%) chance to be a carrier of α²-thalassaemia, and
• one-in-four (25%) chance to be affected by HbH disease. (FIG. 06)

ii. HbH / carrier of α²-thalassaemia

When one parent has HbH disease and the other parent is a carrier of α²-thalassaemia with two non-functional α-genes on one chromosome (cis-position), then each child has, at each pregnancy, a

• one-in-four (25%) chance to be a carrier of silent α-thalassaemia,
• one-in-four (25%) chance to be α²-thalassaemia and,
• an equal risk of one-in-four (25%) chance to be affected by HbH disease or α-thalassaemia major (Hydrops Foetalis). (FIG. 07)

iii. HbH/carrier of α²-thalassaemia

When one parent has HbH disease and the other parent is a carrier of α²-thalassaemia with one non-functional gene on both chromosomes (trans), each child has, in each pregnancy, a one-in-two or 50% chance of being a carrier of α²-thalassaemia or being affected by HbH disease, just like one of his/her parents. (FIG. 08)

iv. HbH / HbH

When both parents have HbH disease there is, in each pregnancy,

• a one-in-four (25%) chance that their child will have α-thalassaemia major (Hydrops Foetalis),
• a one-in-two (50%) chance to have HbH disease, and
• a one-in-four (25%) chance to be a carrier of α²-thalassaemia.

It is also possible for α-thalassaemia to combine with other rare variants affecting the α-gene. Consult your physician or genetic counsellor, or write to TIF in case you need information about any combinations that are not described in this book.
FIG. 04

BOTH PARENTS ARE CARRIERS OF $\alpha^0$-THALASSAEMIA
THALASSAEMIA GENES ON SAME CHROMOSOMES (cis)

FOR EVERY PREGNANCY THE CHANCES ARE:

- 25% UNAFFECTED
- 50% CARRIERS OF $\alpha^0$-THALASSAEMIA (cis)
- 25% HYDROPS FOETALIS
ONE PARENT CARRIER OF α₀-THALASSAEMIA AND THE OTHER A SILENT CARRIER OF α-THALASSAEMIA (α⁺ THAL) THALASSAEMIA GENES ON SAME CHROMOSOMES (cis)

FIG. 05

For every pregnancy the chances are:

- 25% UNAFFECTED
- 25% Silent carriers of α₀-THALASSAEMIA
- 25% Silent carriers of α⁺-THALASSAEMIA (α⁺-THAL)
- 25% WITH HbH DISEASE
ONE PARENT WITH HbH DISEASE AND THE OTHER A SILENT CARRIER OF α-THALASSAEMIA (α⁺ THAL)

FIG. 06

FOR EVERY PREGNANCY THE CHANCES ARE:

25% CARRIERS OF α²-THALASSAEMIA (trans)
25% CARRIERS OF α²-THALASSAEMIA (cis)
25% CARRIERS OF α⁺-THALASSAEMIA (SILENT CARRIER)
25% WITH HbH DISEASE
ONE PARENT WITH HbH DISEASE AND THE OTHER A CARRIER OF $\alpha^0$-THALASSAEMIA (cis)

FOR EVERY PREGNANCY THE CHANCES ARE:

- 25% CARRIERS OF $\alpha^0$-THALASSAEMIA (\(\alpha^+\) SILENT CARRIERS)
- 25% CARRIERS OF $\alpha^0$-THALASSAEMIA
- 25% WITH HbH DISEASE
- 25% HYDROPS FOETALIS
FIG. 08

ONE PARENT WITH HbH DISEASE AND THE OTHER A CARRIER OF $\alpha^0$-THALASSAEMIA (trans)

FOR EVERY PREGNANCY THE CHANCES ARE:

25% CARRIERS OF $\alpha^0$-THALASSAEMIA

50% WITH HbH DISEASE
**HbH DISEASE**
The condition whereby a child inherits only one functional α-gene and three (3) non-functional ones from its parents is associated with a greatly reduced production of α-chains.

In this situation, the excess β-chains, which continue to be produced by the fully functional β-genes, cannot pair up with α-chains to produce common haemoglobin (HbA). Instead, the free β-chains join together to form a new haemoglobin (β4) in the patient’s blood, known as HbH. Although this is not the haemoglobin found commonly in human adult red cells, HbH has the capacity, like common adult haemoglobin (HbA), to deliver oxygen efficiently to the tissues. It is, however, a relatively unstable molecule, and its continuous breakdown results in early death (breakdown) of red cells (haemolysis), which can lead to a moderate to severe anaemia in the affected individual and to other related health problems, such as bone deformation, fatigue, formation of gall stones and enlargement of the spleen, which may vary from mild to severe.

The anaemia is mild in most patients with HbH disease. They generally require no treatment, such as blood transfusion, and they usually lead a normal life. In some cases, the anaemia may be severe and aggravated by certain factors, such as infection, pregnancy or when taking specific medication. As a chronic disorder, HbH disease requires a general annual check-up, follow-up, and, if and when needed, medical treatment in a specialized centre.

**HAEMOGLOBIN BART’S - HYDROPS FOETALIS (α-THALASSAEMIA MAJOR)**
In this situation, the body cannot produce any α-chains and therefore common adult haemoglobin (HbA), which requires the coupling of both α- and β-chains, cannot be produced. Instead, γ-chains, which make up the haemoglobin of the embryo (HbF), join together to form another type of haemoglobin, called HbBarts (4), which does not have any oxygen-carrying capacity and thus cannot sustain life.

Hydrops foetalis results in severe anaemia that affects the baby while in the womb, before birth. An affected foetus appears to grow normally initially, but then develops heart failure, which leads to the swelling of the foetus and the placenta and to a marked increase in the volume of the amniotic fluid (hydramnios). This often leads to premature birth and the baby is usually dead (stillborn) at the time of delivery. The mother may also develop high blood pressure and may have difficulty in delivery. She also has a danger of bleeding after birth, if the contents of the womb are retained. As the life and wellbeing of the mother are at risk, early detection and prevention is essential in this case.

In some extremely rare cases, in-utero blood transfusion has allowed the birth of children with Hydrops Foetalis, who then, however, require lifelong blood transfusion and special medical care.

**INHERITED α- AND β-THALASSAEMIA GENES**
Alpha thalassaemia may be inherited along with β-thalassaemia and abnormal haemoglobins or structural variants from carrier parents. In particular, the presence of β-thalassaemia carrier status in patients with β-thalassaemia major may contribute positively to the clinical outcome of β-thalassaemia major.
Can serious haemoglobin disorders be prevented?
Carrier couples who know of the risk for their children can obtain reliable, detailed and up-to-date information from specialized centres, national health authorities and patients/parents’ support groups.

For the majority of couples at risk for HbH disease, prevention is not necessary, since this condition, despite possible complications such as mild anaemia and gallstones, is compatible with a long and good quality life. If there are reasons to expect a more severe condition, then the doctor will discuss preventive measures with the parents.

However, if the risk is for Hydrops Foetalis, prevention based on prenatal diagnosis and termination of pregnancy is imperative, because of the risk to the mother’s health.

LABORATORY TESTING TO ESTABLISH WHETHER ONE IS A CARRIER
Laboratory testing for thalassaemia and other haemoglobinopathies includes a routine blood test, known as a Complete Blood Count (CBC), which involves measuring the level of haemoglobin and other parameters, such as Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH). These will be lower in individuals carrying the α and β-thalassaemia genes and some other variants.

However, the α-thalassaemia carrier status is difficult to confirm using the above-mentioned laboratory parameters, and even when using Haemoglobin Electrophoresis, which is the method that separates and measures the various types of haemoglobin and which in the majority of cases is used to diagnose β-thalassaemia and SCD. Diagnosis of α-thalassaemia is frequently made by exclusion of other possible causes. Genetic or DNA-based testing alone can give a definitive diagnosis and is also essential for the differentiation between the different kinds of α-thalassaemia carrier states.

HOW IS HbH DISEASE DIAGNOSED?
A child born with HbH disease will show no visible signs of the disease but may develop jaundice early in life. The baby may be diagnosed if a neonatal screening programme is available in the country where the family lives. The diagnosis is difficult to suspect if the parents have not been tested, no prenatal tests were carried out, and there is no other affected child in the family.

It is possible to diagnose HbH disease at a very early stage, but only by means of genetic, DNA-based tests that can identify the genes the child has inherited from each parent (see further below). Other methods include:

i. **Measurement of common haematological parameters by electronic equipment** – red cell counters. HbH disease is suggested where the size and volume of red blood cells and the concentration of haemoglobin inside them are significantly reduced, and the haemoglobin levels are low.

ii. **Blood film and RBC morphology.** Observed under a microscope, the red blood cells of an individual with HbH disease appear paler (hypochromic), smaller (microcytic) and significantly variable in size (poikilocytosis). These changes are more marked in individuals with HbH disease than in carriers of α-thalassaemia.
iii. Chromatographic methods (Electrophoresis or HPLC). These are laboratory processes that separate the different proteins that make up a haemoglobin molecule – such as HbA, HbA2, and HbF. HbH forms a separate fraction and is detected at levels which may vary between 1-40% (usually 8-10%). HbA2, which usually accounts for up to 3% of common adult haemoglobin, will be reduced (by 1-2%).

iv. Genetic or DNA-based methods. These are specialised laboratory methods that can confirm the diagnosis and provide more specific information concerning the mutations (the genetic changes) that cause HbH disease.

TESTING A FOETUS FOR Hb-BART’S – HYDROPS FOETALIS (α-TALASSAEMIA MAJOR)
There are three types of tests that can determine whether a foetus has a severe form of thalassaemia. Also, ultrasound examination of a pregnancy “at-risk” at regular intervals is able to detect the changes characteristic of Hydrops Foetalis. Diagnosis will however be confirmed by:

i. Amniocentesis
This test is performed in the second trimester of pregnancy, after about 15 weeks’ gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother’s abdomen. A small amount of amniotic fluid, containing cells from the foetus, is withdrawn. This is then analysed in the laboratory to determine whether the foetus has Hydrops Foetalis (α-thalassaemia major). The specialist obstetrician will be able to explain and discuss in detail all aspects of this procedure, including potential risks for the couple involved.

ii. Cordocentesis
This is a test performed after 18 weeks of pregnancy. Under ultrasound guidance, a fine needle is inserted through the abdomen into the foetal umbilical cord, through which a small volume of blood from the foetus is aspirated. The blood is analysed in the laboratory. The specialist obstetrician will be best able to explain and discuss with you causes of failure in obtaining pure foetal blood, as well as any other potential risks when undergoing the procedure. Early and specific diagnosis with molecular methods has almost completely replaced cordocentesis, which is now mainly indicated in pregnant women who report late, when CVS is inconclusive.

iii. Chorionic Villus Sampling (CVS)
This is another method of diagnosing haemoglobin disorders in the foetus and can be performed earlier than both amniocentesis and cordocentesis, at about 10-11 weeks’ gestation. Using ultra-
ultrasound as a guide, the specialist obstetrician removes a small sample of cells from the chori-onic villi, i.e. 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 other prenatal diagnosis methods, information on potential risks and benefits of using this procedure are provided to the couple by the specialist obstetrician.

**How is the diagnosis of the foetus made after obtaining samples using the above methods of prenatal testing?**

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

These tests confirm whether the foetus is healthy, a carrier or affected. The couple may decide to either proceed with the pregnancy, accepting that lifelong treatment will be necessary, or to end the pregnancy, if this is possible. If pregnancy termination is the choice, the specialist obstetrician will explain how this is done, depending on the stage of the pregnancy.

Analysis of the sample usually takes about a week. Termination of pregnancy is only justified if clinically severe HbH disease is expected or if Hydrops Foetalis is diagnosed.
SICKLE CELL DISORDERS

INHERITANCE PATTERNS OF SICKLE CELL DISEASE

Haemoglobin S (HbS) / Common adult haemoglobin (HbA)
When one of the parents is a carrier of variant HbS and the other parent carries the common haemoglobin (HbA), each child born to these parents (i.e. for every pregnancy) has a one-in-two (50%) chance of inheriting the HbS variant, i.e. he/she will be a carrier of HbS, just like one of his/her parents.

Other names describing an individual who carries the HbS variant include:
• Carrier of the sickle cell trait
• Individual heterozygous for HbS
• Sickle cell carrier

ABOUT HbS CARRIERS
Carriers of HbS do not have a disease. They have no physical or mental symptoms and do not require a special diet, medical advice or treatment. Their red blood cells are usually similar in size to those of non-carriers, since the quantity of haemoglobin is not reduced. Smaller red cells (microcytic) are sometimes seen in those carriers of HbS who have coinherited α-thalassaemia, a combination common in many populations. Otherwise, the red cells examined under the microscope may be indistinguishable from red cells of non-carriers. Sometimes, altered shapes (poikilocytosis) and cells with pointed ends are seen, but the typical sickle-shaped cells, characteristic of this disorder in the homozygote state, are not often seen in HbS carriers.

The carrier status cannot become a disease over time. Indeed, most individuals will be unaware that they are carriers unless specifically tested.

Carrying haemoglobin S has no effect on health, length or the quality of life. The rare exception to this occurs when a carrier is in a situation of severe lack of oxygen, in which case, pain and blood vessel blockage may be experienced.

Frequently asked questions about carriers

• What about pregnant women who are carriers?
Like other pregnant women, those who carry HbS can become iron deficient and may need extra iron. The anaemia will improve after the baby is born. HbS carrier pregnant women are also more prone to urine infections, as compared to non-carriers or carriers of other haemoglobin disorders.

• Is there any treatment to stop being a carrier?
No, a person who is born carrying HbS will always carry it in his/her genes throughout his/her life.

• Can the sickle cell gene or carrier status be transmitted or acquired at a later stage in life?
The sickle cell carrier status cannot be acquired or transmitted through the environment, transfusion or other means by which people become infected. Carriers who have inherited HbS from their parents could pass it on to their children, through their genes.
Can carriers donate blood?
Carriers may be suitable blood donors if their haemoglobin level meets the national donor inclusion criteria.

How does one know whether he/she is a HbS carrier?
In most cases, simple but specific laboratory tests can identify whether a person is a carrier of sickle cell or of any other haemoglobin disorder.

LABORATORY TESTING
Laboratory testing for sickle cell, as for other haemoglobinopathies, includes a routine blood test known as a Complete Blood Count (CBC), which involves measuring the level of haemoglobin and other parameters, such as the Mean Corpuscular Volume (MCV), and the Mean Corpuscular Haemoglobin (MCH), both of which may be within normal range in HbS carriers, in contrast to those carrying α- or β-thalassaemia.

Another test that is used to determine the carrier state includes a laboratory process known as haemoglobin electrophoresis, which enables the measurement of the quantity of the major (HbA) and minor (HbA2) components of adult haemoglobin, foetal haemoglobin (HbF) and HbS. In the case of HbS carriers, the HbS fraction will constitute up to 40% of the total haemoglobin.

Other ways to diagnose HbS include Isoelectric Focusing (IEF), which is another kind of electrophoresis, High Pressure Liquid Chromatography (HPLC) and Capillary Chromatography, all of which are considered today as methods of reference for screening as well as confirming the diagnosis of haemoglobinopathies.

If the above tests are inconclusive, especially if combinations with other variants or thalassaemias are involved, and do not allow the laboratory scientists to provide a confirmed diagnosis, other more specialised tests are available. These are genetic tests, i.e. tests which examine the genetic material – the DNA of the blood of the individual but also often of other members of the family.

OTHER INHERITANCE PATTERNS

HbS/HbS
If both parents are carriers of sickle cell (HbS), there is at each pregnancy; a one-in-two (50%) chance that the child will also be a carrier of sickle cell, a one-in-four (25%) chance that the child will be completely unaffected, and a one-in-four (25%) chance that the child could inherit HbSS, the full-blown disease known as sickle cell disease (SCD) or sickle cell disorder or sickle cell anaemia or homozygous sickle cell disease. (FIG. 01)

HbS/HbSS
If one parent is a carrier of haemoglobin S (HbS) and the other is a patient with sickle cell disease (HbSS), at every pregnancy there is a one-in-two chance (50%) that the child will be an HbS carrier, and a one-in-two chance (50%) that the child could inherit sickle cell disease (HbSS or SCD).

HbS/β-thalassaemia
If one parent is a carrier of HbS and the other parent is a carrier of β-thalassaemia, at each pregnancy there is a one-in-four chance (25%) that their child could inherit fully functional genes,
BOTH PARENTS ARE CARRIERS OF SICKLE CELL DISEASE (SCD)

FOR EVERY PREGNANCY THE CHANCES ARE:

25% WITH SCD (HbSS)

50% CARRIERS OF SICKLE CELL DISEASE

25% UNAFFECTED
a one-in-four chance (25%) that the child will be a carrier of HbS; a one-in-four chance (25%) that the child could be a carrier of \( \beta \)-thalassaemia, and a one-in-four chance (25%) that the child could inherit the compound haemoglobin disorder referred to as sickle cell/\( \beta \)-thalassaemia (HbS/\( \beta \)-thal). (FIG. 02)

**HbS/HbC disease**
If one parent is a carrier of HbS and the other parent is a carrier of another haemoglobin variant, haemoglobin C (HbC), at each pregnancy there is a one-in-four chance (25%) that the child could inherit fully functional genes, a one-in-four chance (25%) that the child will be a carrier of haemoglobin C (HbC), a one-in-four chance (25%) that the child will be a carrier of HbS, and a one-in-four chance (25%) that the child could inherit a compound haemoglobin disorder called haemoglobin S/haemoglobin C (HbS/C).

**HbS/HbD Punjab**
If one parent is a carrier of HbS and the other parent is a carrier of the variant haemoglobin D Punjab, at each pregnancy there is a one-in-four chance (25%) that the child could inherit fully functional genes; a one-in-four chance (25%) that the child will be a carrier of haemoglobin D Punjab; a one-in-four chance (25%) that the child will be a carrier of HbS; and a one-in-four chance (25%) that the child may inherit the compound haemoglobin disorder referred to as haemoglobin D Punjab/haemoglobin S (HbS/HbD Punjab).

**HbS/HbE**
If one parent is a carrier of HbS and the other is a carrier of HbE, at each pregnancy there is a one-in-four chance (25%) that the child will inherit fully functional genes; a one-in-four chance (25%) that the child will be a carrier of HbE; a one-in-four chance (25%) that the child will be a carrier of HbS; and a one-in-four chance (25%) that the child may inherit the compound haemoglobin disorder called Haemoglobin S/Haemoglobin E (HbS/HbE).

**HbS/HbO Arab**
If one parent is a carrier of haemoglobin S and the other of haemoglobin O Arab, at each pregnancy there is a one-in-four (25%) chance that the child will inherit fully functional genes; a one-in-four (25%) chance that the child will be a carrier of haemoglobin O Arab; a one-in-four chance (25%) that the child will be a carrier of sickle cell; and a one-in-four (25%) chance that the child may inherit the compound haemoglobin disorder called Haemoglobin S/Haemoglobin O Arab (HbS/HbO Arab).

**CLINICAL OUTCOME OF SICKLE CELL DISEASE AND THE COMPOUND HAEMOGLOBIN DISORDERS**

**What is sickle cell disease?**
In this condition, almost all of the haemoglobin in the patient’s blood is HbS. The red cells which contain this variant will change in shape from a biconcave disc to a crescent, or sickle shape, but will also lose flexibility, becoming considerably more rigid. This means that they cannot change their shape easily, as normal red cells with common Hb (HbA) do. As a consequence, passage through small blood vessels is difficult. Loss of flexibility can become serious in conditions of lack of oxygen or in the case of an infection with fever, or when patients with SCD become dehydrated. In these situations, the sickle red cells greatly increase in number and can block the passage of
ONE PARENT IS A CARRIER OF SICKLE CELL DISEASE (SCD) OR HAEMOGLOBIN S (HbS) AND THE OTHER OF β-THALASSAEMIA

FOR EVERY PREGNANCY THE CHANCES ARE:

- 25% WITH COMPOUND HAEMOGLOBIN PATTERN HbS/β
- 25% CARRIERS OF β-THALASSAEMIA
- 25% CARRIERS OF SCD OR HbS
- 25% UNAFFECTED
blood (sickling Sickle cell crisis). As a result, the patient feels pain in the area of the body which is not receiving blood. Such events can be severe enough to damage tissues in joints, spleen, kidneys and even the brain. In addition, as these altered red cells (sickle cells) do not survive in the circulation for as long as normal cells do, and are continuously destroyed, the patients experience a degree of anaemia, which may become severe under certain circumstances, leading to a need for blood transfusion.

Basic indications for red cell transfusion in Sickle Cell Disease are the severity of the anaemia and vascular occlusion. Patients with Hb levels above 7g/dl do not require transfusion. In the case of a vascular occlusion, the aim of transfusion is to prevent or abort intravascular sickling of red cells by means of increasing blood volume or by replacing circulating sickled cells with normal red cells. Exchange transfusion is indicated in programmed major surgery, in eye operations and for the prevention or management of acute vascular occlusion.

As a chronic disorder, sickle cell disease requires treatment in specialized centres aimed at both preventing and managing complications, including the prevention of infections by means of immunizations and the management of pain, which may be severe enough to require hospitalization.

In order to prevent some of the complications effectively, it is necessary to have the patient under continuous observation from early childhood, and in this context a policy of newborn screening is recommended, so that affected children may be identified and followed up from birth.

**Developments in the management of sickle cell disease**

Sickle cell disease affects people in different ways and with variable severity. Some people are mildly affected, whilst others are severely affected, variability occurring even amongst members of the same family.

The reasons for this are not always clear but several contributing factors have been linked with the severity of sickle cell disease. For example, the level of foetal haemoglobin (HbF), which some people continue to produce well into adulthood, is important. Normally, the level of haemoglobin F falls to about 1% by the end of the first year of life and stays at this level right through adulthood. Children with sickle cell disease, however, may go on producing higher than usual levels of haemoglobin F for a longer time. Levels of HbF above 7% appear to be related to fewer sickling crises and fewer complications of sickle cell disease. The level of HbF may be boosted by the use of certain drugs, and this is currently considered as the most promising method for reducing sickling of the blood cells. The advantage of foetal haemoglobin is that it does not have the capacity to sickle and its presence prevents red blood cells from sickling.

**HYDROXYUREA**

Several drugs have been shown to increase the production of foetal haemoglobin. Of these, Hydroxyurea is the most promising and the one that is currently being prescribed. There is good evidence now that Hydroxyurea reduces sickling crises and the need for blood transfusions,
although it may not be suitable for all patients. Hydroxyurea has the potential to reduce bone marrow activity, and this as a consequence increases the risk of infection. It should not be used for patients who are likely to become pregnant, or for those who have difficulty following or adhering to the instructions given for their treatment.

Careful follow-up is needed, with regular visits to the clinic. Hydroxyurea is not a cure for sickle cell disease, but it is an effective treatment for preventing or reducing sickling crises. Its effect will only last for as long as the person is taking the drug.

**HAEMOPOIETIC STEM CELL (INCLUDING BONE MARROW) TRANSPLANTATION (HSCT AND BMT)**

This is the only cure for sickle cell disease at the moment. Transplantation involves taking normal stem cells from a ‘matched’ relative or donor and giving them to the person with sickle cell disease. This is done after the patient has had treatment with strong medicines to wipe out the patient’s own bone marrow, which is responsible for producing the abnormal sickle red blood cells.

Whilst this treatment has been performed successfully on many patients with sickle cell disease, there are several problems involved. It is best done using a matched brother or sister, ideally before the patient develops any complications. As the severity of sickle cell disease can be so variable, it is difficult to justify a high-risk treatment like BMT, where some patients may die, and some may survive but with long term problems. It is essential to carefully select for BMT those that are likely to benefit most or those that are at higher risk of developing serious complications. For example, one test which measures the blood flow in the brain (Transcranial Doppler) can identify patients at-risk for developing a stroke, and so may be used to identify potential candidates for transplantation. The risks and benefits of transplantation must be assessed in each individual case.

As in the case of β-thalassaemia major, it is often difficult to find a relative with a fully-matched bone marrow, making this curative method applicable only to a relatively small proportion of patients (around 16–20%). Rates of success and complication-free survival vary and depend mainly on the patient’s good clinical condition prior to BMT.
GENE THERAPY
In the future, it is likely that gene therapy will be offered for SCD, in the course of which the defective gene is replaced by a normal one. Research in this area has made significant advancements in recent years, but application of gene therapy to humans for a final cure has still a long way to go.

To find out more about these developments, talk to your counsellor or doctor or write to TIF.

HbS/β-thalassaemia is the most common compound haemoglobin disorder. It has a clinical outcome similar to sickle cell disease, which is very different from β-thalassaemia major/intermedia, and which consequently is managed in the same way as sickle cell disease and as described above. The clinical severity of HbS/β-thalassaemia varies just as in SCD.

HbS/HbC, HbS/HbD Punjab, HbS/HbE and HbS/HbO Arab are sickle cell disorders. They are rare and are generally of a mild type. Some persons, however, may develop various degrees of anaemia and may occasionally have attacks of severe pain in joints or other parts of the body. A few may even experience severe health problems and need frequent admissions to hospital. People with these disorders should attend a sickle cell clinic regularly for a check-up and advice.

At present, it is not possible to predict whether a particular couple will have children with mild, moderate or severe HbS/HbC, HbS/HbD Punjab, HbS/HbE or HbS/HbO disorder. It is possible, however, to test a foetus for these disorders early in pregnancy. It is best if “at-risk” couples see a specialist or genetic counsellor to discuss their options. This should ideally be before starting a pregnancy, or at least as early in pregnancy as possible.

HOW IS SICKLE CELL DISEASE DIAGNOSED?
A child born with sickle cell disease will show no visible signs of the disease. The baby may be diagnosed if a neonatal screening programme is available in the country where the family lives. Early diagnosis is particularly important to prevent complications. Screening of newborns is the best way to achieve this, if the parents have not been tested, no prenatal tests were carried out, and there is no other affected child in the family.

It is possible to diagnose sickle cell disease at this very early age by means of simple but specific laboratory tests, such as those described earlier in this booklet for the diagnosis of the sickle cell carrier state.

Special features seen in the laboratory diagnosis of SCD include the presence of sickle-shaped red cells, which constitute around 10% of all the cells, and the presence of HbS reaching levels of around 90-95% in one of the laboratory analyses. When more specific information is needed to clarify or confirm diagnosis, genetic tests are used (as described earlier for confirming the carrier state).

Can Sickle cell disease and other haemoglobin disorders be prevented?
Carrier couples who know of the risk for their children have today a number of choices. They can take steps to make sure that they have healthy children, and that affected children have the best possible care from birth. Their choices are certainly not simple. Every couple, and every citizen in general can obtain reliable, up-to-date information from national health authorities and
patients/parents support groups. Parents who are both carriers, referred to as “at-risk” couples, should know well their risk as early as possible, so that they have enough time to make the decisions that they feel are right for them.

Such couples need to see a haemoglobinopathies specialist (or a specialist genetic counsellor), who will inform them of the exact nature of the risk and what choices are available to them, including prenatal diagnosis in case of a pregnancy to establish whether the foetus is affected or not. An obstetrician specializing in prenatal diagnosis may also provide more detailed information on the procedures available, their risks and benefits, and the possible choices that a couple may make to avoid having an affected child.

**CAN AN UNBORN BABY BE TESTED IN THE WOMB?**

There are a number of tests to find out whether the foetus has a genetic condition, including SCD, and these are called pre-natal diagnosis (PND) tests. They will determine which haemoglobin type the foetus has inherited from the parents.

i. **Amniocentesis**

This test is performed in the second trimester of pregnancy, after about 15 weeks’ gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother’s abdomen. A small amount of amniotic fluid, containing cells from the foetus, is withdrawn. This is then analysed in the laboratory to determine whether the foetus has sickle cell. The specialist obstetrician will be able to explain and discuss in detail all aspects of this procedure, including potential risks with the couple involved.

ii. **Cordocentesis**

This is a test performed after 18 weeks of pregnancy. Under ultrasound guidance, a fine needle is inserted through the abdomen into the foetal umbilical cord, through which a small volume of blood from the foetus is aspirated. The blood is then analysed in the laboratory. The specialist obstetrician will be best able to explain and discuss the procedure, including potential risks, such as causes of failure in obtaining pure foetal blood. Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis, which is now mainly indicated only in pregnant women who report late, when the CVS is inconclusive.

iii. **Chorionic Villus Sampling (CVS)**

This is another method of diagnosing haemoglobin disorders in the foetus and can be performed earlier than both amniocentesis and cordocentesis, at about 10-11 weeks’ gestation. Using ultrasound as a guide, the specialist obstetrician removes a small sample of cells from the chorionic villi of the placenta.
villi, i.e. the 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 (trans-abdominal) or a thin catheter inserted through the vagina (transcervical). The cells are then analysed and a diagnosis made. As with other prenatal diagnosis methods, information on potential risks and benefits of using this procedure are provided to the couple by the specialist obstetrician.

**How is the diagnosis of the foetus made after obtaining samples using the above methods of prenatal testing?**

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

These tests confirm whether the foetus is healthy, a carrier or affected. The couple may then decide, most preferably after discussion with an expert health professional, on how to proceed.

**Other approaches**

Effective prevention cannot rely on the identification of carriers alone. If pregnancy termination following pregnancy diagnosis is not acceptable, other methods that minimise intervention and psychological stress need to be utilised. One such method is pre-implantation genetic diagnosis (PGD), a refined, established laboratory procedure whereby:

i. Cells from a very early embryo (resulting from in-vitro fertilisation) are analysed in the laboratory to confirm the presence or absence of a haemoglobin disorder. Unaffected embryos are then selected for implantation into the womb of the carrier woman.

ii. Unfertilised ova (eggs) which do not carry a haemoglobin disorder or mutation, detected by polar body diagnosis, are selected from the carrier woman and then fertilised using her husband’s sperm. The selected fertilised ova are then introduced into her womb.

PGD is, however, a costly and technologically demanding procedure and several attempts are often necessary for a successful pregnancy.
Thalassaemia was originally considered to be a disease limited to the Mediterranean region, hence its names Mediterranean Anaemia and thalassaemia. The latter is a compound Greek word from thalassa (meaning sea) and anaemia (meaning poor blood), and described the anaemia of individuals living in by the sea and more specifically the Mediterranean Sea. It is now known that Hb disorders occur widely throughout many parts of the world, across southern Europe from Portugal to Spain, Italy and Greece, in a number of Eastern European countries, 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 South America. Thalassaemia is particularly prevalent in areas in which malaria is or was endemic.

It is believed that, in these areas of the world, some people underwent a slight change in their genes – what we refer to in science as a genetic adjustment, or a mutation, which led to important changes in the environment of the red cells. These changes prevented malaria parasites from growing and multiplying in the red blood cells which constitute their hosts, thus giving these people a survival advantage over those in whom this genetic change did not occur. Carriers of thalassaemia (α and β), as well as carriers of other Hb disorders, such as sickle cell, were thus better able to survive malaria than non-carriers. The number of carriers increased significantly over the years in malaria-endemic regions of the world, as large numbers of noncarriers died as a result of severe malaria infections.

For sickle cell disease, it is believed that the sickle cell haemoglobin variant originated in Africa, where it is most commonly encountered, while India is considered as an additional place of origin. From these areas, population migrations have taken the gene to almost all regions of the world. SCD is most prevalent in the indigenous population of Africa, some Middle East and Mediterranean countries.

Population migrations and intermarriages between different ethnic groups have introduced thalassaemia and SCD in almost every country of the world, malaria-endemic or not, including northern Europe and other countries where thalassaemia and SCD did not previously exist and were not known in the indigenous population. According to current epidemiological data, about 7% of the global population carries an affected haemoglobin gene, with between 300,000 and 500,000 affected children born annually. More than 80% of these are born and live in the developing part of the world. About 70% of them have sickle disorder, and the rest have thalassaemia syndromes. A significant number of affected children born in developing countries even today die undiagnosed, misdiagnosed, receiving sub-optimal treatment, or left untreated altogether.

National control programmes are urgently needed to improve prevention, reduce affected births and provide clinical management to improve the survival and quality of life of the patients with Hb disorders across the world.
PUBLICATIONS

1. About Thalassaemia (2nd ed., 2007)
2. Guidelines for the Clinical Management of Thalassaemia (2nd ed. revised, 2008)
10. Sickle Cell Disease (2008)