Thalassaemia is an inheritable disorder of hemoglobin, which results in a reduction in the synthesis of one or more of globin chains of hemoglobin. This disease is also called as Cooley's Anaemia.

Thalassaemia was not known a decade ago but its intensity has increased so much recently that a bill had to be passed in the Parliament to address this disease squarely.

Thalassaemia is carried by over 100 million people throughout the world. WHO estimated that about 7 per cent of world population are carriers of this disorder of hemoglobin. In Pakistan, according to a conservative estimate the occurrence is 5-7%. There is one thalassaemic patient in every third family. Each year about 8000 children are born with thalassaemia major, about 60-70% die by the age of ten. More than 80% develop endocrine problems like diabetes and hypogonadism, 60-70% are hepatitis B and C positive.

The best known hemoglobin abnormality is sickle cell anemia, which is caused by the swap of a single amino acid in one of the chains of protein. Thalassaemia gives protection against the effect of malaria. It has been suggested that possessing one of the abnormal genes that gives rise to thalassaemia provides protection against other blood diseases. This is probably because all the red cells in the body of such a patient are a bit fragile and on entry of malarial parasite inside the red cell, the cell breaks down and the parasite does not grow further. In normal people the parasite keeps on growing and multiplying. In this way people suffering from thalassaemia get an immunity against malaria.

The well known British geneticist J.B.S Haldane in 1948, proposed that individuals who carry one copy of faulty recessive gene (and are consequently symptomless) may be protected against some other disease. This phenomenon is known as “heterozygous advantage”. The best known example of this, as mentioned above, is the sickle cell anaemia.

How Thalassaemia acts in the blood?

Hemoglobin is a protein present in the red cells and is responsible for carrying oxygen from lungs to other tissues. It is composed of two chemical substances which are bound together, “haem” and “globin”. The former containing a central core of iron and the latter, which is a protein, exists as a chain. The body produces a number of different chains. Each molecule of hemoglobin has four globin chains which is attached to its central portion. In adults the normal hemoglobin is called as hemoglobin A. In case the normal formation of globin chain fails, then the make-up of the hemoglobin is affected and results in thalassaemia. The failure can be caused by both either due to the presence of an abnormal gene or by the transcription process, which results into conversion of genetic instruction into production of new protein molecule.

The synthesis of globin chain is controlled by genes, like all other proteins. The gene present on chromosome 16 control the synthesis of alpha globin chain where as beta globin present on chromosome are responsible for the synthesis of beta-globin chain.

alpha thalassaemia is more complex but not that serious. In this case four genes are inherited which are responsible for the production of alpha globin chain. If one or two of these genes are defective then the result is alpha thalassaemia minor. If there are three defective alpha genes, hemoglobin H will be produced, which causes hemoglobin H disease, in which the red blood cells break down and lead to both anaemia and jaundice. This condition is yet not curable, it can however be controlled through occasional transfusion. When all the four alpha chain gene are absent it results into a type of blood which can not support or sustain life and therefore the foetus either aborts or causes still birth.

Out of the two genes inherited from one parent, if one gene is faulty, beta thalassaemia minor is inherited, which is not so dangerous. Clinically thalassaemia major is the homozygous form with high level of Hbf and profound anemia depicted within the first year of life. Thalassaemia minor is the heterozygous state with elevated HbA2 level.

Types of Thalassaemia

In general, thalassaemia is divided into “thalassaemia minor “ and “thalassaemia major”. The former is a harmless and innocent genetic marker, whereas the latter is hematological
disaster of far reaching socio economic health consequences. Two individuals (male & female) suffering from thalassaemia minor if join in matrimony, result into production of children with thalassaemia major. If through regular medical screening, it could be determined that an individual is suffering from thalassaemia minor or one of the related diseases like sickle cell anemia, such a person should not opt to marry another individual with the same genetic defect. In this way the calamity can be avoided. This means that a normal person marrying an individual with thalassaemia minor will produce normal children.

It has been suggested that genetic counselling should be made compulsory and every patient should be screened for genetic diseases.

The most common and enigmatic form of disease is beta thalassaemia major that occurs in offsprings of parents carrying the defective gene. The carrier state which is designated as thalassaemia minor is completely asymptomatic and the sufferer, as mentioned before, may lead a normal life. There is no effect on the synthesis of beta globin chain resulting in decreased hemoglobin and excess of alpha globin genes. The two defects result in transfusion dependent anaemia and characteristic phenotype of the patients.

**Prevalence of Thalassaemia**

Thalassaemia has been reported to occur in areas where malaria is prevalent, such as on the Mediterranean Coast and in the middle or Far East. Thalassaemia may, however, be found almost anywhere in the world.

Cypriots carry the inherited anemia beta-thalassaemia because it defended their ancestor against malaria. That illness has now disappeared from the island, as in time, will thalassaemia, with the incidence of carrier dropping by as much as one percent per generation. Sardinia is a rather traditional Catholic Society in which many marriages risk having a child with thalassaemia. Now 9/10 of the couple who face that predicament know the consequences and when the women has an affected foetus nine-tenth of those chose termination.

**Treatment**

Thalassaemia patients need frequent medical care and attention and sympathy as the disease may lead to many secondary complications. Regular checkup, constant hospitalization, dealing with possible diabetes, osteoporosis, jaundice, cardiac problem may cause anxiety and depression. Thalassaemia patients are usually weak and may need special attention and protection as compared to healthy children in the school. They, being handicapped, require preferential services on priority basis.

Thalassaemia minor does not require any treatment as the patient apparently lives, more or less, a normal life. However thalassaemia major needs blood transfusion, but ultimately it results in iron over load leading to growth retardation and a variety of endocrine and sexual disturbance. Gradual build up of iron, due to inadequate removal, leads also to cardiac hypertrophy, liver disease, damage to pancreas, damage to pituitary and other glands, distortion of skull, delayed sexual maturation resulting into impaired fertility, enlarged spleen, thinning of the bones and vertebrate an increased infection rate.

The choice of treatment is limited such as blood transfusion therapy and bone marrow transplant. Most other treatments are yet ineffective. Some patients may need daily treatment to allow the iron to be excreted safely in the urine. Antibiotics may also be used to counter infection. In some cases spleen may also be removed.

In families with history of anaemia the disease may be expected in all infants under the age of two, especially in some ethnic groups and in general population with symptoms of Beta-thalassaemia major.

**Diagnosis**

Using simple tests the presence of gene for thalassaemia may be determined. The blood of the foetus may also be examined at about 20th week into the pregnancy to determine if there are any beta chain present. After confirming the diagnosis with complete blood count, red cell indices, peripheral smear and hemoglobin electrophoresis /HPLC, further diagnostic studies may be performed.

**These tests may include:**

a) HLA typing of patient and siblings, if bone marrow transplant is required

b) Screening of HIV, HBS Ag, Anti Hepatitis-C virus.
Transfusion haemosiderosis is the major cause of late morbidity and mortality in thalassaemia. Iron accumulation is the consequence of blood transfusion as well as increased iron absorption from blood probably secondary to ineffective erythropoiesis. Each 500 ml of transfused blood contains 250 mg iron. In poorly chelated thalassaemia major patients that is a massive build up of iron in blood. Non-transferrin blood iron (NTPI) is a potentially toxic component of the plasma iron which results in free radical generation causing tissue damage. Those parents who do not receive iron chelation therapy, the accumulation of iron will continue progressively and by the time 20-25 gm of iron is accumulated, clinical presence of iron toxicity may become evident. Iron, as has already been mentioned, damages all the vital parts of the body and endocrine system. Myocardial siderosis is one of the causes of death, in under treated patients, which occurs due to congestive cardiac failure and arrhythmias.

Liver disease is caused by direct accumulation of iron. Excess of melanin and hemosiderin deposition in skin gives a grey appearance.

Iron Chelation Therapy

Iron chelation therapy is very important in thalassaemia management. It should start at an early stage when serum ferritin exceeds 1000 mg / L or after about fifteen transfusion.

Before 1980, the treatment was expensive and difficult as the only preparation available in Pakistan was desferrioxamine (DF) in injectable form, either in the skin or intravenously. The DF is a highly specific iron binding hydroxamic acid as the standard treatment. It is ineffective when administered orally. It has to be injected 5 times a week. The most promising orally effective iron chelator is deferiprone as reported by an international group of oral iron chelator (ISGOIC). However it has some major side effect such as agranulocytosis arthritis and skin changes secondary to zinc deficiency.

The procedure of treatment with desferrioxamine was difficult and expensive as the patient had to be admitted in the hospital to receive the treatment. Since early 90’s locally assembled cheap infusion pumps were introduced in the market, which made iron chelation available to out patient from various thalassaemia centres in the country.

Monthly transfusion (5 times a week) and treatment with the drug desferrioxamine has a cost reaching six to seven
thousand dollars a year.

**Bone Marrow Transplant**

Bone Marrow transplant has been recently introduced in Pakistan and is the only curative treatment available. However, the availability of a compatible donor is quite problematic. The closest perfect match is usually a sibling in which case only one in every four sibling will fulfill the required immunological criteria.

The first successful bone marrow transplant was successfully performed in 1981 in Seattle, Washington, to a 16-month old boy referred by the university of Pavia, Italy. By the year 2000, the number of such transplant rose to over 2000 throughout the world.

Bone Marrow transplant, which ensures permanent cure, costs about thirty to fifty thousand dollars a year. This being a very high cost of treatment, is beyond the affordable range of common man.