Chapter 1: INTRODUCTION

1.1: Introduction to Genetic disorders.

Genetic diseases, their etiology and management have been a cause of concern to medical scientists for centuries. Infact, the paucity of knowledge in this field has been a major hurdle. These diseases, though individually rare, collectively form considerable medical, social and financial burden. More so, particularly in developing countries, it is stated that, when one would conquer infectious diseases, genetic diseases would come to the forefront and play major role in producing human morbidity and mortality. Hence genetic factor plays important role in health and disease.

Thus in the twentieth century, we find ourselves lying amongst infectious problems of developing world interspersed with genetic diseases.

At present in India, majority of the health problems are related to infectious diseases. With the progress of science and literacy, people are becoming more and more aware about their hygiene, resulting in reduction of infectious diseases. Henceforth majority of the emerging health problems will be of organic or genetic in origin.

The occurrence of a genetic disease in a family is so devastating to the parents and the patients that it poses a tremendous financial, emotional and social burden, which is life long. The gravity of the problem is very intense and it masks the rarity of these diseases as compared to other
common diseases. Therefore, genetic diseases as a group form a major health problem all over the world including our country.

Genetics is the science of systematic study of inheritance, and disorders that are inherited or conditions in which genetic factors play an important part are known as genetic disorders. A recent classification according to D.J. Weatherhall lists, Genetic diseases into 5 different groups. These are,

1. Chromosomal disorders.
3. Polygenic multifactorial disorders, congenital malformations.
4. Disorders of mitochondrial DNA. Cytoplasmic inheritance.
5. Disorders due to somatic cell mutations.

1) Chromosomal disorders - Normal individuals have 46 chromosomes, 23 pairs in which each member of the pair is of either maternal or paternal origin, 22 pairs are autosomal while one pair determines the sex of an individual. Chromosomal disorders are caused due to qualitative or quantitative abnormality of the chromosomes and may affect either autosomes or sex chromosomes or rarely, both simultaneously. A given abnormality may be present in all the body cells, or there may be two or more cell lines of which one or more are abnormal. The latter situation is termed mosaicism. Quantitative abnormality is due to altered
Chromosome number from normal 46 and arise chiefly through the process of nondisjunction (failure of paired chromosomes or sister chromatids to separate). Some well known numerical chromosomal disorders are the Trisomy 21 (Down syndrome), Klinefelter syndrome -47XXY, Turner syndrome -45X0, Trisomy 13 (Patau syndrome), Trisomy 18 (Edward syndrome). Qualitative abnormality arises due to alteration in some part of the chromosome, the stable type of aberration are translocation, deletion, duplication, inversion and isochromosomes. The unstable types are dicentrics, acentrics and ring. (Wolf syndrome, Prader-Willi syndrome, Wilm tumour, aniridia syndrome, etc).

Chromosomal abnormalities are among the best defined causes of fetal loss or congenital disease. The frequency of spontaneous abortion is estimated to be between 15 and 20 percent of all pregnancies, and of these approximately 50 percent are associated with chromosome abnormalities.

The frequency of chromosomal abnormalities at birth is approximately 5.6 per 1000, of these about 2 per 1000 are due to a variation in the number of sex chromosomes. 1.7 per 1000 to variation in numbers of autosomal chromosomes and 1.9 per 1000 to are major chromosomal rearrangements.

2) Single gene disorder—Disorders occurring due to defect in single gene of an individual. In the 1988 edition of Victor Mc Kusick's Mendelian inheritance in man, the clinical geneticist's bible, 2208 proven mutant phenotypes and an additional 2136 probables are listed, a
grand total of 4344 monogenic diseases. Of the defined phenotypes 1443 are classified as autosomal dominant, 626 as autosomal recessive, and 139 as X-linked.

Autosomal dominant disorders - dominant otosclerosis, adult polycystic kidney disease, familial hypercholesterolaemia, osteogenesis imperfecta, etc.

Autosomal recessive disorders - hemoglobinopathies, cystic fibrosis, cystinuria, galactosaemia, Gaucher disease, etc.

Sex linked disorders - Glucose-6-phosphate dehydrogenase deficiency, red-green colour blindness, haemophilia A and B, Duchenne muscular dystrophy, etc.

3) Multifactorial disorders - Multifactorial disorders result from the complex interaction of both genetic and environmental factors. This includes common chronic diseases of adulthood such as peptic ulcer, diabetes mellitus, Ischaemic heart disease, Epilepsy, Schizophrenia, Congenital malformation and mental retardation are the disorders occurring during foetal or neonatal life.

Congenital malformation follows a multifactorial or polygenic form of inheritance. Parents are usually normal and therefore it is assumed that several genes are involved in the development of these regions. The phenotype results from the balance between the number of defective and normally active genes that are inherited. Only when the balance towards abnormal genes exceeds a critical threshold the malformation occurs.
Congenital malformations comprise 8% of the perinatal mortality in India, that ranks fifth in perinatal mortality. I.C. Verma have compiled the hospital based data on congenital malformations which shows that an average of 20.2 per 1000 births are having major congenital malformations and of these 6.15 are due to neural tube defects.

Mental retardation has a complex basis that includes monogenic and polygenic disorders, chromosomal abnormalities and a number of ill defined environmental factors.

4) Cytoplasmic disorders - Mitochondrial DNA is transmitted through cytoplasm of the ovum. The mitochondrial DNA is responsible for some of the rare diseases. It follows a pattern of maternal inheritance but children of both sexes are affected and subsequent generations show the trait as autosomal dominant. Mitochondrial myopathies, Leber’s optic neuropathy and mitochondrial encephalopathies are the examples of cytoplasmic disorders.

5) Disorders due to somatic cell mutations - Over the last few years it has become obvious that many forms of cancer result from acquired abnormalities of the genetic machinery of cells. Throughout our lives we are constantly renewing many of our tissues and this requires the orderly division and maturation of the particular cell populations involved. It is now clear that cell division and differentiation is controlled by batteries of genes, both within the cells themselves and in related cell populations.
There is increasing evidence that malignant transformation; that is the inability of a particular cell population to divide and mature in an orderly and restrained fashion, results from a breakdown of these genetic mechanisms. Thus cancer is thought to result from a series of acquired mutations involving these fundamental cellular regulatory mechanisms. Even more interestingly, it appears that we may inherit genes that make us more likely to develop a particular cancer following a mutation of this type in a somatic cell.

From single gene disorders, hemoglobinopathies (inherited disorders of hemoglobin) are a major group with an estimate of $2.42 \times 10^6$ heterozygotes throughout the world and probable births of the affected individuals per year are 217800. Hemoglobinopathies is divided into three different groups. First there are the structural hemoglobin variants. Second, there are the thalassemias, which are characterised by a reduced rate of production of either alpha or beta globin chains and which are, therefore, divided into the alpha and beta thalassemias. Finally, there is a group of conditions in which there is a hereditary persistence of fetal hemoglobin.

Over 400 different human structural hemoglobin variants have been described, of which 95 percent are due to single amino acid substitution in the corresponding triplet codon of the globin gene DNA. It can be calculated that there are 2583 potential single base substitutions for the 141
residues of the alpha chain and the 146 residues of the beta chain. Of these 1690 would result in an amino acid replacement, but only a third would cause a change in charge which would allow the abnormal hemoglobin to be identified by electrophoresis, about 45 percent of these potential variants (1) have already been discovered.

In India, hemoglobin S, hemoglobin D and E are commonly occurring beta globin chain variants while hemoglobin Koya Dora and hemoglobin Rampa are alpha chain variants occurring sporadically. Out of these total heterozygotes about 25% traits are of Sickle cell hemoglobin.

Sickle cell disease is the first molecular disease described, characterised by sickle shaped red blood corpuscles in deoxygenated state. It is an autosomal recessive disorder. This is caused by an amino acid replacement at 6th position from glutamic acid to valine due to a point mutation in 6th codon (CTC-CAC), in beta globin gene of normal adult hemoglobin. Beta globin gene is located on chromosome number 11. This gene is well characterised and different mutations present with sickle cell hemoglobin has been described from Africa, Saudi Arabia, and the Indian subcontinent. Sickle cell mutation makes hemoglobin insoluble and polymerises in deoxygenated state causing the cells to become sickle in shape. After oxygenation, the cell regains its shape. When a cell sickles and unsickles repeatedly, the membrane is affected and ultimately cell becomes irreversibly sickled. Irreversible sickle cells have
short intracellular lifespan and are readily removed from circulation causing anaemia when present in homozygous state. Distorted (sickled) red cells also occlude vessels, causing recurrent infarctions, especially of the lungs, bones, and spleen. The marrow shows compensatory hyperplasia, and the spleen is enlarged in early childhood, but becomes impalpable later when subject to recurrent infarction. Affected persons are also prone to pneumococcal infections and to salmonella osteomyelitis.

Thalassemia is a disorder of hemoglobin synthesis, where there is unequal synthesis of one of the globin chains which causes anaemia. Thalassemia in combination with sickle cell hemoglobin as a doubly heterozygous condition is as severe as sickle cell anaemia, or even more.

First report of sickle cell hemoglobin is from an (7) African migrated to USA in 1910. When we review world literature based on the population genetic survey work and published work from hospitals, the sickle cell hemoglobin is present amongst the Negro race of equatorial Africa, East Africa, migrated African population to North America and Europe, Saudia Arabia, Northern Greece, and Central and Southern India.

In India, it is first reported from Nilgiri hills by Lehman and Catbush, and in Assam by Dunlop and (8,9) Mazumdar. High frequency of sickle cell gene has been found in tribal population of the Nilgiri’s and several tribes and scheduled caste groups of Gujrath, Madhya Pradesh,
Orissa and Andhra pradesh.

In the state of Maharashtra, there are few reports of presence of sickle cell gene, mostly confined to scheduled caste and scheduled tribe groups. However, majority of tribal groups remained uninvestigated and no planned survey work was undertaken. Almost all reports were based on sickling test only. From available hospital reports it is found that there is marked difference in clinical course of sickle cell hemoglobinopathies. Some cases had severe clinical manifestations while others were of benign type, and few cases had intermediate clinical course. Prevention is the only remedy for genetic disorders. It can be done at two stages, 1) Marriage counselling and/or 2) Prenatal diagnosis in first trimester for high risk couples. Hence work was undertaken with following aims and objectives.
1.2 Aims and Objectives

1) To find out prevalence of sickle cell hemoglobin in different population groups of Maharashtra.

2) To study the incidence of sickle cell anaemia in different population groups, as a public health problem and to estimate differential mortality due to sickle cell anaemia.

3) To study the clinical and biochemical features of sickle cell anaemia.

4) To study the clinical course of sickle cell disease in different population groups.

5) To establish a method for prenatal diagnosis of sickle cell anaemia using advanced molecular genetic techniques.