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Genetics and Public Health in Post-Genomic Era

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Abstract: Although clinical genetics had its roots predating Mendel's discovery, the clinical case histories were not documented in terms of genes or loci. Even when such defects were shown to follow Mendelian rules of transmission, this was not sufficient to manage the problem. It was ouly when cytogenetic and more precisely biochemical or molecular basis of disorders was known, the field established its status all over the world. In post genomic era, the scope has widened and genetic service has become almost a necessity for public health.

Key words: Genetic disorders, biochemical, molecular markers, genetic counseling, gene therapy, ethics

INTRODUCTION

There are at present about 13000 human diseases which are genetic in nature and the list is growing day by day (McKusik, 1989). Approximately one in 100 new born is expected to have a genetic disease. These diseases spring from abnormal genetic material called morbid genome that result into an organic defect and thus can't be cured permanently like the other pathological ones (Hamosh *et al*., 2002). If we add other genetic disorders like chromosomal, multifactorial, mitochondrial and somatic cell disorders i.e., cancers, the number reaches more than 15,000 (Thomas, 2004). In a country like India, with population of one billion and birth rate of about 47 children per minute, a child is born with a genetic disorder every two minutes. This entails a great burden of genetic disorders which are unfortunately ignored due to higher infant mortality rate, various types of infections and malnutrition (Verma, 1986). Nevertheless, genetic disorders are seen in 3% of all pregnancies, 5-10% of all pediatric hospital admissions and 1 in 100 adults (single gene or chromosomal and affect multiple organ systems and requires frequent admissions (Purandare and Desai, 2004). Therefore, genetic service constitutes the major bulwark of public health concern in all developed as well as developing countries.

HISTORICAL

With the gradnal increment of the basic knowledge of biology, medicine has also increased its frontiers. The earliest healing consisted of only magical and religious charm (McKeown, 1988) based on oral tradition or scriptural knowledge (Pasternak, 2005). This was to be replaced by primitive naturopathy or enviroumental healing, followed in turn by germ theory, which ultimately revolutionized the study of infectious diseases (Evans and Brachman, 1993). However, when the antibiotics and the surgicals brought the curve of infectious diseases down in the west, new group of diseases started to become prominent (Kumar, 2004). This group of diseases is called genetic disease, caused by defect in the hereditary material of man at various levels cellular, sub-cellular or molecular (Emery, 1984). Hence hereditary diseases pose the greatest challenges, as they are invulnerable to

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antibiotics, not caused by germs. Ottenburg and Epsteira started the first genetic clinic in the US (1910) followed by Roberts in the UK (1946) though delayed in Germany and India.

Medical geneticists (Emery and Rimon, 1983; Jackson and Schimke, 1983) for the sake of convenience, have classified all diseases into three categories-purely genetic, genetico-environmental and purely infectious ones (Connor and Fergussonsmith, 1997). The former are those diseases which are transmitted from the parent to the offspring in Mendelian fashion, or through chromosomes at fertilization, viz., sickle-cell anemia, haemophilia, thalassaemia, Down's syndrome, Turner's syndrome and Kleinefelter's syndrome (OMIM, http://www.ncbi.ndm.nih.gov./entrez/query.figi.db). The infectious ones are caused by pathogens like virus, bacteria, fnngi, protozoans and helminths viz., malaria, typhoid, kala azar, cholera, small pox (major tropical diseases) and are carried most often by vectors under unhygienic living conditions. They can be cured by various antibiotics and antipathogens. The middle ones are mid-way between the two-these diseases can be expressed nnder certain environmental conditions, but the susceptibility to disease is inherited viz., schizophrenia, diabetes mellitus, hypertension and even cancer (Ramalingaswamy, 1986).

GENETIC SYSTEM

How, then, do genetic diseases arise? These arise due to defective genotypes which control the body traits or phenotypes (Schinzel, 2001). The body of all organisms are made up of microscopic units called cells, each of which consists of 23 pairs of threads called chromosomes (total number is 46 and called diploid number half of which, haploid one, comes from the father and the other half from the mother. The chromosomes (Miller and Therman, 2001) are carriers of hereditary material, made of protein and DNA (the hereditary material, which is the only physical link between the parents and the offspring), which is really a double helical spiral structure, consisting of two threads, made of sugar, phosphate and nitrogenous bases, also called nucleotides.

Again, for the simplicity of Nature, there are only four types of different nucleotides: adenine, guanine, cytosine and thymine, however, it is the linear arrangement of nucleotides along the DNA thread that is the code of heredity and constitutes gene. There are thus 3×10^9 base pairs in each cell which is called the total genome of the organism (Pasternak, 2005). Genes are therefore, units of heredity, made of DNA and passed from parent to the offspring through chromosomes in germ cells and functionally they direct the synthesis of all proteins in body through a rigorous dogmatic information-flow viz., DNA to RNA to protein, determining the traits. Thus, whatever, characteristics (qualitative or quantitative) of the individnal appear (phenotype) these are controlled by the snm total of all genes (genotype) and can't be altered during the entire life time of the individnal viz., health, complexion, height, weight, pnlse-rate, blood characteristics and even intelligence and personality. There are thus 10^{14} cells, 3.5 pgm of DNA, 3×10^9 base pairs, 3×10^4 genes and 10^5 proteins/cell (McKonky, 1983). About 1200 loci are mapped. Hereditary diseases, therefore, arise due to morbid genome or chromosomal defects or both.

Origin

With regards to their origin, hereditary diseases are said to arise due to mutations which can be of the following types: Chromosomal, Monogenic and Polygenic disorders. There are genetic disorders due to mitochondrial genome also which is sometimes spoken as 24th chromosome.

CHROMOSOMAL

These disorders are most severe (Afzal and Verma, 1986) and usually result into physical and mental abnormality, infertility and physical dysmorphism (Gersen and Keagle, 2005). The most lethal

ones are aborted, still-born, or die perinatally (Book, 1995). Therefore, the frequency of chromosomal disorders in the population shows decrease with the increase in the age of the subjects (Gustin *et al*., 2003). Most of these disorders result due to abnormality in the sexual reproduction, during meiosis, especially among the mothers, causing loss or gain of chromosome numbers, aneuploidy, or even multiplication of haploid number (polyploidy) due to multiple fertilization (Sankaranarayanan, 1979). Still other changes are there due to structural changes in individual chromosome (structural changes) (Guttenbach *et al*., 1997) not in the set of chromosomes (karyotypic). In yet the third type, normal variations in chromosome structures occur without much abnormality, a phenomenon called as genetic polymorphism. Below is given a simple account of various causes for chromosomal disorders in man (Borgaonker, 1997) (Table 1).

Karyotypic

The whole diploid set of chromosomes (2n = 46 in man) is called a karyotype (Mittleman, 1995). Due to normal meiosis, 23 chromosomes in the sperm and 23 in the egg, combine together during fertilization to form a zygote with 46 chromosomes. Being two XX, the zygote is female, with XY, it is male. Following changes can be seen in the number of chromosomes due to pre-or post-fertilization events (Table 2).

Euploidy

Due to an egg being fertilized by two sperms (n, n) simultaneously, a triploid (3n) zygote can be formed (Niebuhr, 1974). Sometimes, an abnormal diploid (2n) sperm can fertilize a normal egg (3n) or a diploid egg (4n) and so on. Penta-ploids and hexaploids can be formed similarly. However, none are

Table 1: Chromosomal disorders (Euploidy and aneuploidy)

Autosomes	Sex-Chromosomes
Numerical abnormalities	Turner syndrome
Trisomy	45, X
8 trisomy	46, Xi (Xq) and mosaics of Xq cell line
9 trisomy	46, Xdel (Xq) and mosaics Xq cell line
13 trisomy (Patau syndrome)	Mosaics 45X/46 XX 45X/47 XXX
18 trisomy (Edwards syndrome)	Mosaics 45, X/46 XY
21 trisomy (Down syndrome)	Other (del, Xp, X mosaics)
22 trisomy	Klinefelters syndrome
Polyploidy	47, XXY
Triploidy	48, XXXY
Tetraploidy	49, XXXXY
Structural abnormalities	Mosaics
Partial trisomy	Others
1 q trisomy	Polysomy X-females
2 q trisomy	47, XXX
3 q trisomy	48, XXXX
5 p trisomy	49, XXXXX
7 q trisomy	Mosaics
9, p, trisomy	Polysomy-Y
10q trisomy	47. XYY
14q trisomy	Others
22q trisomy	
Deletion (partial monosomy)	
4 p deletion syndrome	
5, p, deletion (cry-du-chat) syndrome	
9 p deletion	
13q deletion	
18p deletion	
18q deletion	
21q deletion	
22q deletion	

born alive and die *in utero*. A few living tetraploid rabbits have been found and among plants multiploids are a usual feature (as they are propagated asexually).

Aneuploidy

However, due to meiotic non-disjunction, pair of chromosomes fail to separate into two daughters and we have abnormal gametes-having 24 or 22 chromosomes each (DeGrouchy and Turleau, 1984). However, if a gamete with 24 chromosomes gets fertilized during fusion with opposite gamete of normal type (i.e., 23) ouly, a zygote with 47 chromosomes results (24 + 23 = 47) (Holmes and Martin, 1993). Similarly various combinations can follow (23 + 22 = 45, 22 + 22 = 44, 25 + 23 = 48, 26 + 23 = 49). These can be designated thus.

(a) Nullisomy-Complete loss of any chromosome-pair, fatal and do not survive, 2n = 44, 42 and so on (found in abortuses), (b) Monosomy- Some of the chromosomes are unpaired, 2n = 45. One such condition is there for X-chromosome called X-monosomy (Turner's syndrome), (c) Trisomy-Some of the chromosomes are present thrice, 2n = 47. The most prominent defect is mongolism (Azfer and Afzal, 1995), as the child affected is mentally retarded and has low body resistance and is also called Down syndrome, after its discoverer. Here the chromosome number 21 is present thrice. There is another condition, called *Kleinefelter's syndrome*, where a male karyotype consists of an excess X chromosome and is 47, XXY. Trisomy for chromosome 13 is called *Patau's* syndrome and trisomy 18 is called *Edward's syndrome* (Table 1, 2), (d) Tetrasomy and Pentasomy: Such cases are quite frequent for sex-chromosomes. Thus, 48 XXXY, 49, XXXXX, 48 XYYY, the last case is invariably males with extremely violent nature, often as notorious criminals.

Mixoploidy

Sometimes, there are more than one type of cells in the body, a phenomenon known as mixoploidy (Edwards *et al*., 1994). Such individuals display mosaicism (when after fertilization) and chimaerism (at the time of fertilization). Such individuals usually have one cell normal and the other is monosomic or trisomic and so on. The body anomalies are not severe but defects are still recognizable. Further, depending upon the nature of chromosomes, the defect may be sex-chromosomal, when it is there in sex-chromosomes (X or Y) and autosomal, when it is for the rest of the chromosomes. Thus, Turner (45X) and Kleinefelter (47 XXY) cases are to be called sex-chromosomal and Down ones as autosomal defect. Mixoploids for sex-chromosomes are often intersexes and are mentally abnormal.

Structural Abnormalities

Yet in another type of chromosomal abnormalities, the gross number of chromosomes remains the same, but individual chromosomes are altered, either due to breakage of a segment (depletion), duplication of a segment, exchange and fusion of segments (translocation) and mid reversal of the sequence of segments, called inversion. A large number of examples can be cited here:

Table 2: Incidence of some chromosomal disorders

Spontaneous abortions	Newborns (Absolute rate)	
40% apparently normal	Balanced translocational	1/500
60% abnormal	Unbalanced translocational	1/2000
Trisomy 30%	Pericentric inversion	1/100
-45 X, 10%	Trisomy 21	1/700
Triploid 10%	Trisomy 18	1/3000
Tetraploid 5%	Trisomy 13	1/5000
Others 5%	47, XXY	1/1000 males
	47, XYY	1/1000 males
	47, XXX	1/1000 females
	45, X	1/10000 females

Deletion

Deletion of a part of chromosome is mostly deleterious, causing monosomy for the given segment, various changes are denoted thus, 4p-(Wolf-Hirsschhorn Syndrome), 5p-(Cri-du-Chat Syndrome). Apart from these, there are few microdeletion of chromosomes causing various diseases, Prader-Willi syndrome (15 q 12). Die George (22 q 11), Aniridia (11 p 13), multiple endocrine neoplasia (20) retinoblastoma (13 q 14) and Langer Giedon Syndrome (8 q 23). Besides these, there are a few chromosomal disorders like Fanconi's anemia (showing breaks and gaps in chromosomes) and Bloom's syndrome etc.

Duplications

Such changes are not harmful, though, new functions of genes can follow, as is the case with Bar-eye in *Drosophila* and other disease in man (Taylor *et al*., 1997).

Inversions

These are suppressors of crossing over, causing non-viability of gametes and hence result into various types of infertility and reproductive wastage (Chandley *et al*., 1987).

Translocation

It is usually harmful, leading to unbalanced genotype. In chronic myeloid leukemia, part of the chromosome 22 q is lost (22 q-) and is attached to chromosome 9(9 p+). Such changes in chromosome are brought about by environmental agents, called mutagens and the phenomenon is then called mutagenesis (Rowley, 1998). In yet third condition, two acrocentric chromosomes can be fused forming a long metacentric chromosomes. If it is a balanced karyotype involving no loss or gain of the chromosomal segments, the individual is normal and carrier, however, during meiosis, the translocated chromosome goes to one gamete ouly, causing excess of that chromosome (23, but really amounting to 24) and in other one loss of one chromosome is there (22). On fertilization by normal gamete (23), abnormal zygotes are formed (23 + 23+1 = 47), or other abnormal one (23+22 = 45). Such cases are infertile. The recent technique of using probes for detecting the structural anomalies is called Fish (Fluorescent In situ hybridization) and is much more sensitive (Joos *et al*., 1994; Kakazou *et al*., 2003).

Other Changes

Fragile X-Associated Mental Retardation (Martin Bell Syndrome)

Here the patients are males with MR (Badaruddoza *et al*., 2000) eularged testes (30-50 mL in place of 20 mL), Ring and X-chromosome with fragile site (4-60% of cells show thin region on Xq 27.3) (Turner *et al*., 1996).

Ring Chromosome

When the two ends of a chromosome are deleted, the sticky ends can join together to form a ring chromosome. A ring without centromere is lost. Hence rings are seen in deletion cases (Turner's) (Kooztolamyi, 1987).

Isochromosome

It is a chromosome whose one entire arm is lost, while the other arm is just double (duplicated) (Suijkarbuijk *et al*., 1991). It arises due to transverse division of centromere and half chromatid of each goes to one side (Xqi is isochromosome which can cause Turner's syndrome).

Centric Fragments

Additional small metacentric fragments are seen (Yang *et al*., 2000). These are familial.

Chromosomal Breakage Syndrome

These are the result rather than the cause of the diseases. This spontaneous rate of chromosomal breakage is due to several single gene disorders, inherited as autosomal recessive trait viz., premature cancer. In ataxia telangiectasia, the chromosomes are radiosensitive and end-to end fused chromatids are found (11q22.3). Bloom syndrome is characterized by increased sister chromatid exchange due to somatic recombination (15q26.1), Xeroderma pigmentosum (Lehman, 2003) is characterized by defective DNA-repair following UV light exposure (9q22.3, 2q14.3, 3p25.1, 19q13.32). Similarly, in the disease known as Fanconi's anemia (Howlett *et al*., 2002), undue sensitivity to DNA-cross-linking agents are also found to change breakage syndrome (Weemaes *et al*., 1981).

MONOGENIC DISORDERS

Unlike chromosomal mutations visible under microscope, monogenic disorders are conditions arising due to altered genes (point mutation) on a part of chromosome called *locus* (Shows *et al*., 1987). These are real genetic disorders which are transmitted from parent to the offspring in Medelian fashion. These may have three types of inheritance patterns.

Dominant

When at least single allele is sufficient to cause the effect, it is called dominant (Wilkie, 1994).

Recessive

When both the alleles are necessary to cause the effect.

Codominant

When both the alleles get equal share in the expression. Again, depending upon the nature of chromosomes involved, these may be designated as-(i) Autosomal: When the gene responsible for a trait is present on the autosome, (ii) Sex-linked: When the gene is present on a sex-chromosome X or Y. Hence, we have an X-linked inheritance or Y-linked (Holandric) one.

Roughly speaking, there are about 30,000 genes in the cells (Wain *et al*., 2002a, b) of which 3000 are known and 450 genes are mapped to be present on their specific chromosomes (Table 3). About 115 of these are present on X-chromosome alone. About 200 genes are causing inborn errors of metabolism and all are recessive (Heterozygotes are normal). There is a rule of thumb that dominant disorders do not have enzyme deficiency and recessive disorders are caused mainly due to the absence of enzymes in cells. These and other disorders have characteristics McKusick catalogue number so as to avoid phenotypic or genotypic duplicity of some common disorders. Some of these disorders can be listed here viz.

Structural Protein Disorders

Autosomal dominant: Achonodroplasia, Apert syndrome, Congenital spherocytosis, Hereditary angioneurotic oedema, Hereditary thrombophilia, Huntington diseases, Hyper-cholesterolemia, Marfan syndrome, Multiple endocrine neoplasia, Multiple exostoses, Myotonic dystrophy,

Table 3: Assignment for single gene traits

	1966	1975	1986	1994
Autosomal dominant	837	1218	2201	4458
Autosomal recessive	531	947	1420	1730
X-linked	119	171	286	412
Y-linked	-	-	-	19
Mitochondrial	-	-	-	59
Grand total	1487	2336	3907	6678

Neurofibromatosis, Treacher Collins syndrome, Tuberous spherosis, Von Hippel-lindau disease. Autosomal recessive: Cystic fibrosis, Friedreich ataxia, Haemochromatosis, Hepatolenticular degeneration.

Inborn Errors of Metabolism

Many of the enzyme deficiency diseases are leading to inborn errors of metabolism (Clarke, 2002; Stanley, 1996; Hsu and Rivkeer, 2005), first studied by Sir Archibald Garrod, an English physician. These are all recessive.

Congenital adrenal hyperplasia (White and Speiser, 2000): 21-hydroxylase deficiency: Deletion of active cytochrome 450 genes involved in steroid 21-hydroxylation, excessive salt loss, virilization of the female with ambiguous genitalia, elevated urinary ketosteroids and pregnanetriol, elevated serum 17α-hydroxy progesterone and ACTH. Linked to MHC gene on chromosome 6. Cystinuria (Goodyer *et al*., 1993): Increased excretion and reduced intestinal absorption of cystine, lysine, arginine and ornithine. Galactosaemia: Absence of galactose 1-phosphate-uridyltrans-ferase (GALT) causing accumulation of galactose in the urine, neonatal weight-loss, hepatomegaly, jaundice. Locus on 9 p (Holton *et al*., 1981). (iv) Gaucher's disease (Grabowski *et al*., 1998): Glucosidase assay gives negative result, reduced leucocyte contents, infantile progressive neurological illness, with hepatosplenomegaly. Locus on chromosome 1. Mucopolysaccharidoses: 4 types (7 types also known); Hurler's syndrome (type-1), deficiency of alpha-L-iduronidase, mucopolysa-ccharidurea. Hunter-syndrome (type 2), deficiency of sulpho-iduronide sulphatase, muco-polysacchariduria, sanfilppo-syndrome (type 3), deficiency of heparen sulphatase or N-acetyl-alpha-D-glucosaminidase, mucopolysaccharidurea and Morquio-disease (type-4), deficiency of fibroblast 6-sulpho-N-acetyl hexosaminidosulpha-tase, coarse facies in infancy, corneal clouding, short stature, progressive mental retardation (Oeijord, 2002). Phenyl Ketonuria (PKU): Deficiency of hepatic phenyl alanine hydroxylase, elevated blood and urine phenyl alanine, mental retardation due to myelinization of neurons, locus on chromosome-12 (Platt, 1997). Tay-Sachs disease: Reduced serum hexosaminidase A, Cherry red macular spot, progressive neurological abnormalities from late infancy (Taketomi *et al*., 1997). Zell-weger syndrome (Cerebrohepatorenal syndrome) (Gomella and Cummingham, 2003): Reduced dihydroxy acetone phosphate acyltransferase (DHAP-AT) in skin fibroblasts and platlets, marked hypotonia with hepato-megaly, increased urinary pipecolic acid and dicarboxylic acids, increased ration of C26 and C22 chain-fatty acids some other disorders include Autosomal co-dominant, Alpha-antitrypsin deficiency: Protease inhibitor activity and typing by isoelectric focusing, juvenile cirrhosis (10%), pulmonary emphysema (Crystal, 1996). X-Linked Dominant, (x) Incontinentia pigment: Infancy marked by vesicular skin rash, followed by irregular whorled pigmentation, partial alopecia, hypodontia, mental retardation; hemizygote males die (Caputo and Tadini, 2006). Rett syndrome: Onset about one year, hand washing, automatisms (Amir *et al*., 1999). Androgen insensitivity (testicular feminization) syndrome: Reduced cell-binding of testosterone and dihydrotestosterone carrier detected by 5-dihydrotestosterone in genital skin fibroblasts (Balen *et al*., 2004). X-Linked Recessive: Haemophilia A: Factor VIII less than 30% of normal, recurrent haemorrhage, locus on Xq 28, largest gene (186 kb, 26 exons) (Lakich *et al*., 1993). Haemophilia B: Factor IX less than 30% normal, locus Xq 27, 34 kb size, 8 exons (Giannelli *et al*., 1996). Lesh Nyhan syndrome: Reduced red cell hypoxanthine guanosine phosphoribosyl-transferase (HGPRT), later mental retardation, self-mutilation, (allopurinol lowers uric acid) locus on Xq 26, 42 kb, nine exons (Anderson, 2003). X-Linked Muscular dystrophy: DMD (Duchenne muscular dystrophy DMD), progressive proximal muscle weakness, marked elevation of serum creatine kinase, abnormal electromyogram and muscle biopsy, BMD (Becker mascular dystrophy)-progressive muscular weakness in late childhood, calf pseudohypertrophy death about 20 years, locus on Xq 212. The incidence for some of these disorders are given in Table 4 (Bushby, 2001).

Table 4: Incidence of certain single gene disorders

Disorders	Dominant traits	Frequency/ 1000 births	Recessive traits	Frequency/ 1000 births
Autosomal	Dominant otosclerosis	3.0	Cystic fibrosis	0.5
	Familial hypercholesterolemia	2.0	Recessive mental retardation	0.5
	Adult polycystic kidney disease	1.0	Congenital deafness	0.2
	Multiple exostoses	0.5	Phenylketonuria	0.1
	Huntington's disease	0.5	Spinal muscular atrophy	0.1
	Neurofibromatosis	0.4	Recessive blindness	0.1
	Myotonic dystrophy	0.2	Adrenogenital syndrome	0.1
	Congenital spherocytosis	0.2	Mucopolysaccharidoses	0.1
	Polyposis coli	0.1	Others	0.3
	Dominant blindness	0.1		
	Dominant congenital deafness	0.1		
	Others	1.9		
	Total	10/1000		2/1000
X-**Linked**	Xg blood group		Red-green colour	800/10000
	Pseudohypoparathy-roidism		Fragile associated	MR 5.0
	Vitamin D resistant rickets		Non-specific X-linked	MR 5.0
	Incontinentia pigment		Deuschene muscular dystrophy	MR 3.0
	Rett syndrome		Beccker muscular dystrophy	MR 0.5
			Haemophilia A (Factor VIII deficiency)	MR 2.0
			Haemophilia B (factor IX)	MR 0.3
			X-linked icthyosis	MR 2.0
			X-linked gamma globulinaemia	MR 0.1
	Total			817.9/10,000

Table 5: Gene deletion (partial/total) in human single gene disorders

Structural gene	Diseases
Factor VIII	Haemophilia A
Factor IX	Haemophilia B
Growth hormone	A type of growth hormone deficiency
21-hydroxylase deficiency	Congenital adrenal hyperplasia
Hypoxanthine-guanine	Lesch-Nyhan
Phosphoribosyl transferase	Syndrome
Phenylalanine hydroxylase	Phenyl ketonuria
Low density lipoprotein receptor	Familial hyper-cholesterolemia
α1 (I) collagen	Severe osteogeneses
α2 (I) collagen	Imperfecta
Red cone pigment	Proton colour blindness
DMD locus	Duschene muscular dystrophy
BMD locus	Becker muscular dystrophy
CGD locus	Chronic granulomatous disease
Steroid sulphatase	X-linked ichthyosis
Antithrombin III	Antithrombin III deficiency

Molecular Pathology

Various genetic disorders, monogenic in nature, are attributed to distinct abnormalities of a protein-product of physiological significance. Such can be characterized as molecular pathology, caused due to a change in the DNA itself (Killeen, 2004). These are point mutations (Antonarkis, 1998) and can be of the following types.

In deletion (Table 5), some gene is lost, causing the absence of its product. Different types of thalassaemias are the result viz., α-thalassaemia and β-thalassaemia (Steinberg *et al*., 2000). Normal haemoglobin is a metalloprotein, having a haem-group, containing an iron-pigment and 4 protein-chains, two each of α and β type ($\alpha_2\beta_2$) having 141 amino acids and 146 amino acids, respectively. There is 2% of A_2 haemoglobin (HbA_2) also containing $\alpha_2\delta_2$ chains. In foetal life, foetal haemoglobin (HbF) has $\alpha_2\gamma_2$ chains. However, other embryonic haemoglobins, Hb Gower I ($\alpha_2\gamma_2$), Hb Gower II ($\alpha_2\varepsilon_2$) and Hb Portland ($\alpha_2\gamma_2$) are also there. The α chains are coded by alpha-gene cluster on short arm of chromosome 16 for 2 chains of α protein four α genes are present in each diplodid cell, 2 genes per chromosome 16. For β gene, only one gene per chromosome 11 is enough.

Table 6: Molecular pathology of Beta-Thalassaemia

Mechanism	Examples
Point mutation	C¬T88bp to 5' side of beta globin.
a) Defective transcription (Promoter mutants)	A¬G 29 bp to 5' side of beta globin
b) Defective mRNA processing (Defective splincing)	G¬A at intron 1, position 1
	G¬A at intron 2, position 1
	G¬A at intron 1, position 5
	(Asiatic Indians)
Abnormal new splice sites	Betaglobin codon 26
	GAG¬AAG creates new site in exon 1 (hemoglobin E)
Internal intron changes	G¬A at position 110 of intron (Mediterraneans)
	C¬T at position 654 of intron 2 (Chinese)
Polyadenylation mutants	AATAAA-AACAAA
	(American Black)
c) Defective translation premature chain termination	Beta-globin codon 17 A¬T
(none-sense mutations)	Beta-globin codon 39 C¬T
	Gln¬Stop (Mediterranean)
Deletion	
a) Defective transcription	619 bp partial deletion (Asiatic Indian)
	Haemoglobin lepore,
b) Defectrive mRNA-processing	25 bp deletion at 3' end of intron 1
c) Defective translation frameshit mutants	Two base deletion at beta-globin codon 8
	One base deletion at beta gloibin codon 16
	Four base deletion at beta globin codon 41 and 42
Insertion	
a) Frameshift mutants	One-base insertion at beta-globin codons 8/9
	One-base insertion at beta-globin codon 71/72 (Chinese)

Table 7: Types of Haemoglobinpathies

Type	Molecular defect	Phenotype
Hb	Point mutation	B6Gflu¬val (sickle cell disease)
Hbc	-do-	B6Glu¬lys
HbE	-do-	B26 Glu¬lys
HbM Boston	-do-	B 58 His¬Tyr (Methaemoglo-binaemia)
HbM Saskaton	-do-	B63¬his¬tyr (-do-)
HbM constant spring	-do-	141 stop¬Glu-(Alpha thalassaemia)
Hb Wayne	-do-	Deletion at α-139-Frame-shift

The α-thalassaemias (Nagel, 2000) are produced due to reduced alpha-globin synthesis, caused by deletion of one or more of the α-globin genes. The β-thalassaemias are due to reduced (β + or β-) or absent (β^o) β-globin synthesis. Over 30 types of changes in DNA cause this (Table 6). Such patients are suffering from anemias; carriers are less affected; homozygotes are severely affected and can die. Some times due to deletion of segment between γ and β gene, no-β chain is produced, only γ-chain is there and this leads to persistence of γ-chain or foetal haemoglobin in adult life. Very, often various compounds can co-exist together.

There are various types of changes in the DNA base, mainly single base substitutions, causing different types of haemoglobins (Table 7). These are HbS (B_6 Glu¬Val), HbC (B_6Glu-Lys), HbE (B_{26} Glu-Lys), HbM Boston (B_{58} His-Tyr), HbM Saskatoon (B_{63} His-Tyr) and Hb Constant spring (α_{141} stop-Gln) and Hb Wayne (Deletion at α_{139}-Frameshift). The disease caused by these abnormal haemoglobins are sickle cell anemia, (HbS) and methaemoglobinaemia (Hb Boston and Hb M Saskatoon) and also α-thalassaemia (Hb constant spring). There are more than 430 abnormal haemoglobins, many do not interfere with the function of haemoglobin and are therefore, asymptomatic, but others are critical and causing various forms of anemia listed above (Halkier, 1992). Mitochondrial disorders: Human mitochondrial genome is circular with 16,568 bp, encodes for 2 ribosomal RNAs, 22t-RNAs and 13 proteins. The proteins are involved in OXPHOS functions forming ETP chain sub-units. Some mitochondrial protein and peptides are coded by nuclear genes also. Each mitochondrion has 2-10 genomes. Mitochondrial DNA mutations affect 1 in 10,000 live

birth and generally get acutely felt in high metabolic organs in brain, heart, muscle and kidney. Some of these diseases are LHON (optic neuropathy), neuropathy, kearns sayre syndrome etc (Wallace, 1992).

POLYGENIC DISORDERS

These are characterized by more than one gene producing the effect and are complex in inheritance (Rao and Province, 2001). Those below 15 genes are called oligogenic traits and beyond 15 are put as polygenic. About 75% of inherited human disorders at birth are multifactorial. These include mental retardation, neural tube defects (Spina-bifida, anencephaly), hypertension, diabetes mellitus, other congenital malformations and even cancers (Gorlin *et al*., 2001; Roberts and Pembrey, 1985). Enviroument is very important for the expression of these traits and their manifestation is determined by heritability ratio etc. Usually twins show similarity of expression (concordance) or may show differences in their expression (discordance) (Spector *et al*., 2000). Further, their expression shows positive correlation with the degree of genes shared in common between the relative, the first degree relatives (parent to child, sib to sib) show greater changes than the second degree relatives (grand parent to grand child, nephew or niece, to aunt and uncle) and so on. Furthermore, these may be characterized as continuous traits, viz., height, weight, intelligence, red cell size, blood pressure or as discontinuous traits, like malformations (Cleft-lip and palate, pyloric stenosis) or adult diseases (Rheumatoid arthritis, epilepsy, schizophrenia, manic depression etc. (Epstein and Belmaker, 2002).

The expression of the trait depends upon a balance between minor and major genes as normally active genes, ouly when the balance passes a limit (threshold), malformation occurs. The frequency of malformations in populations equals the proportion of the population to the right of threshold (1%). This curve (liability curve) shifts to the right increasing the threshold for the first degree relatives (increased frequency of affected person, 4%), or more severe malformation (bilateral, in place of unilateral, have curve also shifted to the right). This is sometimes related to sex (more males), age and ethnicity etc.

Congenital Malformations

A malformation is a primary error of normal development resulting in changed morphogenesis of an organ (Gibson and Potparic, 1995; Wilson and Cooley, 1994) or tissue. These may be single or multiple (14% of neonates have single minor 3% have single major, 0.9% have multiple major) and their frequency lowers from conception onwards (7-10% of spontaneous abortions are caused by major malformations). A deformation arises in the embryonic period by unusual mechanical forces. Some of these are caused by maternal illness, congenital infection, drugs, X-ray, alcohol, besides chromosomal, monogenic and unknown (idiopathic) reasons. Examples of malformations can be given: congenital dislocation of the hip, club-foot, epicanthic folds, simian crease, umbilical hernia and major ones like those in brain (microcephaly, neural tube defect) heart (Badaruddoza *et al*., 1994), (ventricular atrial), septal defect, aortic stenosis, renal agencies, renal hyperplasia and displasia. Kidney (bilateral) post-axial polydactyly, thyroid dysgenesis various multiple congenital malformations include Beckwita-Wiedemann, CHARGE association, de-lange, Noonan syndrome, William's syndrome (Wang, 1998).

Common Chronic Diseases of Adulthood

These include Cancer, Ischaemic heart disease, Systemic hypertension, Diabetes mellitus, Bronchial asthma, Peptic ulcer, Ankylosing spondility, Rheumatoid arthritis, Psoriasis, Glaucoma, Multiple sclerosis, Epilepsy, Affective psychosis, Schizophrenia, Parkinson disease, Dementia, Aging, Receptor-protein related disease, Susceptibility to enviroumental mutagens and toxins, Immunity related diseases etc. (Stanbury *et al*., 1983).

Table 8: Mapped human cellular oncogenes

Gene symbol	Original identification	Human chromosomal location
ABL	*Abelson murine leukaemia virus*	9q34
AKT1	*Murine thymoma virus*	14q32
BLYM	*Avian lymphoma virus*	1p32
ERBA1	*Avian erythroblastic leukaemia virus*	17p 11-q21
ERBB	*Avian erythroblastic leukaemia virus*	7p12-p14
ERV1	*Endogenous retroviral seqnence 1*	18
ETS1	*E.26 acute avian leukaemia virus*	11q23-q24
FES	*Feline sarcoma virus*	11q25-q26
FMS	*McDonough feline sarcoma virus*	5q34
FOS	*Murine, FBJ Osteosarcoma virus*	14q21q31
HRAS1	*Harvey rat sarcoma 1 virus*	11p15
HRAS2	*Harvey rat sarcoma 2 virus*	X
INTI	*Murine mammary tumour virus*	12 pter-q14
KRAS1	*Kirsten rat sarcoma 1 virus*	6 p23-q12
KRAS2	*Kirsten rat sarcoma 2 virus*	12 p12
MET	*Osteosarcoma cell line*	7q22.3-q23.1
MOS	*Moloney murine sarcoma virus*	8q11-q22
MYB	*Avian myeloblastosis virus*	6q15-q24
MYC	*Avian myelocytomatosis virus*	8q24
MYCL	*Avian myelocytomatosis virus*	1p32
NGL	*Rat neuroglioblastoma*	17q21-q22
NMYC	*Human neuroblastoma*	2p23-24
NRAS	*Neuroblastoma RAS virus*	1p-22
RAF1	*Murine leukaemia virus*	3p 24-p25
RAF2	*Murine leukaemia virus*	4
REL	*Avian reticulo endotheliosis virus*	2
SIS	*Simian sarcoma virus*	22q12-q13
SKI	*Avian sarcoma virus*	1q 12-qter
SRC1	*Avian sarcoma virus*	20q 12-q13
SRC2	*Avian sarcoma virus*	1p 34-p36
YES1	*Yamaguchi sarcoma virus*	18 q 21
YES2	*Yamaguchi sarcoma virus*	6

Cancers (Sinkovics, 2004)

Certain genes called proto-oncogenes are responsible for normal growth and development of tissues. When they go berserk, cancerous growth results. Such protooncogenes are turned into active forms of oncogenes due to point mutations or by viral agents (Andrieu *et al*., 1997). Such oncogenes have been isolated from all kinds of tumors viz., lung, breast, gonad etc. Activation takes place by position effect, mutation and translocation etc. Two types of such oncogenes are recognized-cellular oncogenes (c) from host or V-oncogenes from the retrovirus. Over 30 oncogenes have been isolated, cloned and mapped (Table 8). Most of them are having normal functions-produce growth factor (Sis produce platelet derived growth factor), receptor for growth factors (erb-B) produces epidermal growth factor receptor) and ras family have tyrosine phosphokinase activity, related to hormone and growth factor receptors (Futreal *et al*., 2004). The oncogene in tumour cell produce their increased protein product or new types of proteins. Any mutations can fire this protoncogene to oncogene and produce cancer viz., by virus, by chromosomal rearrangements, by mutagens, by carcinogen etc. For example, translocation of c-abl oncogene from normal site of 9q34 to chromosome 22q11 causes, a specific sequence (bcr) or 5.8 kb in size to be added to it, causing a novel protein resulting in chronic myeloid leukemia (CML) cells, a blood cancer. In Burkitt's lymphoma, a translocation of 8q24 and either of 14q32, 2p11 or 22q11 causes shifting of myc oncogenes to 14q32, where it is activated by enhancers or heavy chain immunoglobin genes (Cooper, 1995; Pimmatel, 1987). Yet another type of cause of cancer or any genetic disorders is genomic imprinting (inactivation) of useful genes (David and Price, 1993).

Pharmacogenetic Disorders (Asymptomatic or Ecogenetic disorders)

There are many conditions, mostly due to single gene disorders, which are asymptomatic, but get expressed when environmental triggers (agents) induce them (8). Such are mainly related with drug exposures and can be listed as: (a) Glucose-6-Phosphate dehydrogenase deficiency: Determined by a gene near the long arm of the X chromosome (X_q28), it is important for generaion of NADPH, required for reduction in all cells. About 315 variants are known (multiple allelism) having normal, reduced or even enhanced enzyme activity. It is endemic in malarial belts. Hemizygous males are asymptomatic, but use of antimalarial, sulphonamide, nitrofurantoin, aspirin, probenecid, chloramphenicol, quinidine, naphthalene etc. and broad beans cause acute haemolytic anemia, (b) Acute intermittent porphyria (AIP): Determined by gene near tip of the long arm of chromosome 11, it is responsible for reduction in uroporphyrinogen-1-synthetase activity, an autosomal recessive. Exposure to drugs like barbiturates, sulphonamides, griseofulvin, diphenyl-hydantoin, starvation, infection lead to pophyric crisis viz., abdominal pains, vomiting, red-urine, neuropathy etc., (c) Succinyl-choline sensitivity: Serum-cholinesterase is produced by gene on chromosome 3, with two-codominant alleles E_1a and E_1a when given general anaesthetic (with succinyl choline or suxamethonium), cholinesterase activity is absent, causing, prolonged muscle-paralysis, (d) Hyperthermia of anaesthesia, (hyper-pyrexin): Choline or halothane induced hyperpyrexia, hypertonia and CK increase and death, (e) Susceptibility to infectious agents like Haemophilus influenze type B in Alaskan Eskimos is related with genetic polymorphism of uridine monophosphate-kinase 3 (Brachman and Evans, 1998).

Molecular Data Bases

A list of molecular data base is presented (Table 9). These are mostly freely available on the internet, though paid sites are also there. These data bases are used for bioinformatics purpose for genomics and functional genomics studies. The data bases are mainly a bibliographic resources, cellular regulation, chromosome aberration, comparative genomics, gene expression, gene identification and structure gene mutation, gene sequences, genetic and physical maps, genetic disorders, genomic sequences, intermolecular interactions, metabolic pathways, protein motifs protein sequences, protein structure, proteome resources, RNA sequences, transgenic organisms (Baxevanis, 2003).

MANAGEMENT

Such a vast range of genetic disorders (Afzal and Verma, 1990) though encountered ouly sporadically in populations, are still a significant cause for the major body ailments and need to be controlled. Though, complete cure is not possible in all cases, as is the case with other diseases, many steps have been taken to prevent or even cure many of them. Following approaches have been made.

Genetic Counselling

Counselling is a communication of information or advice about inherited conditions. It starts with the person affected called a proband and the individual which seeks such information is called a consultand, usually the parents or close-relatives. It includes history and pedigree construction, examination, diagnosis, counselling session and a follow up. A correct pedigree is very helpful in deciding the pattern of abnormality, usually autosomal dominant traits show vertical transmission, recessive ones show horizontal one and X-linked ones have oblique pattern. Physical examination is needed to note any dysmorphism, with accurate measurements and dermatoglyphics. Care should be taken to exclude population variations and note identifiable syndromes. Diagnosis should include appropriate chromosomal, biochemical or DNA diagnosis, wherever needed. Chromosomal diagnosis is suspected in dysmorphic features, unexplained MR, multiple congenital anomalies, recurrent miscarriage, primary infertility, miscarriage, etc. Counselling should be non-directive, all information

Table 9: Molecular databases

Database	URL	Description
ALFRED	http://alfred.med.yale.edu	Allele frequencies and DNA polymorphisms
Alzheimer disease mutations	http://molgen.www.uia.ac.be/AD mutations/	All gene mutations related to Alzheimer disease
Array express	http://www.ebi.ac.uk/arrayexpress	Microarray gene expression data
Atlas of genetics and Cytogenetics in oncology and hematology	http://www.infobiogen.fr/services /chromcancer	Genes, cytogenetics and clinical features of cancer and cancer-prone diseases
Cooperative human Linkage center	http://gai.nci.nih.gow/CHLC/ chromosomes http://dip.doe-mbi.ucla.edu	Integrated genetic and marker maps of human Database of Interacting Proteins (DIP) Protein-protein interactions
dbSNP	http://www.ncbi.nlm.nih.gov/SNP/	Single-nucleotide polymorphisms
DNA data Bank of Japan (DDBI)	http://www.ddbj.nig.ac.jp	All known nucleotide and protein sequences
EMBL nucleotide Sequence database	http://www.ebi.ac.uk/embl.html	All known nucleotide and protein sequences
Ensembl	http://www.ensembl.org/	Annotated information on eukaryotic genomes
ExPASy molecular Biology server	http://ca.expasy.org	Expert protein analysis system. Liuks to protein databases
GDB	http://www.gdb.org	Human genes and genomic maps
GenAtlas	http://www.citi2.fr/GENATLAS/	Human genes, markers and phenotypes
GenBank	http://www.ncbi.nlm.nih.gov/	All known nucleotide and protein sequences
GeneCards	http://bioinfo.weizmann.ac.il/cards/	Integrated database of human genes, maps, proteins and diseases
GeneClinics	http://www.geneclinics.org/	Medical genetics information resource
Genew	http://www.gene.ucl.ac.uk/cgi-bin /nomenclature/searchgenes.pl	Nomenclature for human genes
HugeIndex	http://hugeindex.org	mRNA expression levels of human genes in normal tissues
HuGeMap	http://www.infobiogen.fr/ services/Hugemap	Human genome genetic and physical map data
Human gene mutation database	http://www.hgmd.org	Links of locus-specific mutation databases
Kyoto encyclopedia of Genes and GFenomes (KEGG)	http://www.genome.ad.jp/kegg	Metabolic and regulatory pathways
MITOMAP	http://www.gen.emory.edu/ mitomap. html	Human mitochondrial genome
Online mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/Omim/	Catalog of human genetic and genomic disorders
PROSITE	http://www.expasy.org/prosite	Biologically significant protein patterns and profiles
Protein information Resource (PIR)	http://pir.georgetown.edu	Comprehensive, annotated, nonredndant protein sequences
PubMed	http://www.ncbi.nlm.nih.gov/PubMed/	Abstracts of journal articles
RefSeq	http://www.ncbi.nlm.nih.gov/ Locus LInk/refseq.html	Nonredndant sequences from genomes, genes, transcripts and proteins
SNP consortium	http://snp.cshl.org	Single-nucleotide polymorphisms
Stanford microarray database	http://genome-www.stanford.edu/ microarray	Raw and normalized data from microarray experiments
Swiss-Protein/TrEMBL	http://www.expasy.ch/sprot	Protein sequences
UCSC genome browser	http://genome.ucsc.edu/	Genome assemblies and annotation

and options (future pregnancy with prenatal diagnosis, artificial insemination by donor, *in vitro* fertilization, contraception both reversible and irreversible) should be dealt and feeling of guilt or stress should be removed. More than one person at risk in the family should also be examined. Follow up programme is also needed. Abortions are permissible in different countries. Usually, precaution is taken in considering consanguinity, genetic heterogeneity and non-penetrance and exposure to irradiation (0.01 grays or less during early stages of pregnancy adds risks of 1/1000 to the foetus for congenital malformation, MR or cancer (Faraone *et al*., 1999; Harper, 1993).

Prenatal Diagnosis

It includes all types of embryonic and foetal diagnosis, in about 8% of all pregnancies and it provides safer pregnancy with genetically-disease-free offspring in 93% of the case. It includes both invasive and non-invasive (ultrasound and radiography techniques) and is asked if a foetus is at risk. Amino-centesis is a time-tested procedure of aseptic withdrawal of amniotic fluid at 16-18 weeks of pregnancy (containing 180 mL of liquor with maximal number or viable cells). Ten to twenty milliliters of fluid is taken and tested for foetal sexing, foetal karyotyping, foetal enzymatic defects (metabolic disease); biochemical assay and foetal DNA diagnosis. Foetal sexing for aborting child of undesirable sex is banned. About 70 inborn errors of metabolism can be diagnosed, rise in alpha-foetoprotein (AFP) of aminotic fluid is an index of neural tube defects, (an increased maternal serum AFP can also be seen) level of 17-hydroxyprogesterone is abnormal in 21-hydroxylase deficient adrenogenital syndrome of glycosaminoglycans in muco-polysacchari-dosis and isozymes of alkaline phosphatase and gamma-glutamyl-transpeptidase in diagnosis of cystic fiborsis. Foetal DNA obtained from amniotic cells (directly or in culture) can be used for Restriction Fragment Length Polymorphism (RFLP) test. Over 1% of risk is there for abortion. Foetoscopy is an endoscopic visualization of the foetus at 18-20 weeks of gestation, it is useful for foetal blood sampling, foetal skin or liver biopsy (risk of abortion 5%). Among the invasive techniques, Chorionic Villus Sampling (CVS) is possible at 8-12 weeks, carefully gnarded under ultrasound and 10-50 mg or tissue can be taken out. Direct chromosome preparation (without culture) is possible within 24 h. DNA analysis of biochemical tests can be completed within 12-weeks and termination of pregnancy can be performed within the first trimester itself. Ultrasonography is unhazardous for the foetus, giving image of the congenital malformations of head, limbs, genitalia etc., radiography of foetus from 10 weeks is useful in diagnosis of skeletal dysplasia. In a limited number of cases, foetal therapy is possible giving better prognosis viz., direct blood transfusion at foetoscopy for rhesus iso-immunization, to contain severe rhesus haemolytic disease (Abrausky, 2003; Trent, 1995; Pritchard, 2003).

Population Screening (Pritchard, 2003)

The objective of population screening is to detect those at risk for genetic disease for the entire population. This is possible ouly in few cases, where the nature of disease is well known, frequency is higher, early diagnosis is conducive to pre-symptomatic therapy, sensitivity is higher to test false positives and benefits outweight the costs (Khoury *et al*., 2003). At present it is done for haemoglobinopathies, (Asia) Tay-Sachs disease and thalassaemias for certain groups of populations. Prenatal, neonatal and adult screening programmes are available, prenatal screening for chromosome abnormalities in adult women, alpha-foetoprotein screening in neural tube defects and ultrasound screening for congenital malformation in at risk pregnancies are a common practice. Phenyl-ketonuria (Guthrie Bacterial inhibition assay) and congenital hypothyroidism, are included in neonatal screening (Charrow *et al*., 2000; Levy and Alberts, 1998, 2000). Quite ambitious planning for presymptomatic screening of adult can detect individuals at risk and even colectomy can be helpful in case of future development of polyposis coli.

Prevention and Treatment

The ultimate aim of all such studies is the prevention and treatment of genetic diseases. Thus any approach which limits the very genesis of disease is called as prevention, while the correction of disease is called treatment. Hence, we also follow here the dictum, prevention is better than cure. There is an intimate relationship between prevention and therapy for both acquired (A) and genetic (B) diseases. Thus we can approach the control in the following order: (a) a disease can be treated symptomatically, (b) abnormal genotype should be prevented by prenatal diagnosis and termination (Secondary prevention), (c) abnormal genotype can be treated by genic correction itself (gene therapy),

(d) abnormal genotypes are not allowed to be produced at all, by counselling and checking any fertilization (primary prevention). Here the stage given in (a) and (c) can be discussed (Herson and Ammerman, 2001).

Symptomatic Treatments (A) Dietary Therapy

PKU (Phenyl Ketonuria)

This is a disease of amino acid metabolism in which the enzyme phenyalanine hydroxylase required for conversion of phenyl alkaline to tyrosine is absent and the individual shows developmental abnormality, brain damage and even cerebral fracture. The disease can be checked by supplying rationed diet with low or even free phenyl-alanine (Roth and Townsend, 2003).

Galactosaemia

This is caused by intolerance of galactose as the individual lacks the enzyme galactose-1-phosphate uridyl transferase. Severe retardation, eye cataracts (leading to blindness), liver degeneration etc., follow. Such defects can be checked by drinking milk without any galactose in it. However, both these disease are to be diagnosed early and dietary control has to be immediately applied, to make the babies grow normally.

Drug Therapy

Some diseases are curable by administration of drugs too.

Lesch Nyhan Syndrome

Due to the deficiency of HGPRT (hypoxanthine guanosine phosphoribosyl transferase), an enzyme required for DNA purine metabolism, Uric Acid is accumulated and the stones get deposited in kidney, causing cerebral palsy, severe developmental retardation, aggressive and self mutilative behaviour and even kidney destruction etc. Allopurinol is the drug used for recovery (Joseph, 1997).

Removal of Deleterious Products

Wilson's Disease

This is caused by the accumulation of copper in the body and can be cured by pencillamine (Drewer, 2001; Vogel and Motulsky, 1997).

Replacement of Missing Product

Certain diseases are caused by lack of certain hormones and growth factors etc. these may consist of one or the other of many such defects.

Adrenogenital Syndrome

Caused by lack of androgens and hence is curable by steroids.

Pituitary Dwarfism

Lack of growth hormone from pituitary and can be cured by supplying growth hormone.

Congenital Hypothyroidism

Here the cretinism results due to the lack of thyroxine (hormone from thyroid) and can be cured by exogenous supply of the hormone.

Haemophilia

Here factor VIII is deficient, the clotting of blood is imperfect and blood loss is severe Factor VIII is to be supplied (Duzzard, 2000).

Diabetes

Insulin is given; replacement is never ideal and sometimes insulin treatment may not check comma, blindness, kidney failure, CV disorders, heart-attack etc.

Enzyme Replacement Therapy

Previous methods dealt with treating the disease at symptomatic level. As is well-known, 200 inborn-errors of metabolism are known. Two broad categories of such ailments are well known-Vitamin responsive inborn errors of metabolism like organic academia which are characterized by an anomaly of a co-factor biotin required for degradation of organic acids, which appears in blood, causing death (hence hundred percent lethal). Other example is from methyl malonic academia, caused by Vitamin B_{12} disturbance. Such diseases can be treated with supply of enzymes, like in mucopoly-saccharidoses, lipodoses etc. (Gaucher's diseases, Hurler's disease, Tay Sach's disease etc.). However, this approach is limited due to a number of reasons, viz., to get purified enzyme is very difficult, often they do not pass through blood-brain barrier, these are rarely taken up by the reticuloendothelial system, characterized by cells responsible for removal of foreign-invaders and organisms and finally, female carriers have enzymes present in their cells (Saftig, 2005).

Tissue Transplantation Therapy

In some cases, tissue or even organ transplantation can be attempted to supply missing products directly in place of enzyme therapy. The greatest danger in this is immunological rejection, which is responsible by immunosuppressive drugs like cyclosporin. Before attempting tissue transplantation, facility for tissue matching must exist. The patient, a sixteen year old boy, improved sufficiently showing no thalassaemia. The tissue, usually transplanted, are mainly bone marrow, liver, pancreas etc. (Freeman and Widner, 1998).

Gene Therapy

McKusik (1989) presents the position of the loci causing disease in his treatise, Morbid Anatomy of Human Genome, the ultimate vice in man himself which is his greatest enemy in his survival. On an average every individual carriers six such genes (enemies), but for the presence of the other normal genes to suppress the former, the individual escapes genetic disorders (Brock, 1993). The whole gamut of gene-therapy requires different aspects of gene isolation, gene introduction and gene function in the corrected cells to completely start normal functioning (Hui, 1994). Some of the recent developments in these fields can be presented here (Friedmann, 1999).

Isolation of the Gene

A mutant gene has first to be completely characterized in the laboratory to know its properties. This needs extraction of DNA followed by localization of gene through complementary DNA/RNA hybridization systems called probes. The nucleotide sequencing can be done and through gene cloning, multiple copies can be obtained (Drlica, 2004).

Introduction of the Gene

This would require normal genes to be introduced into cells by various methods, such as by using vehicles viz., through liposomes (Gao and Huang, 1993), red blood cells, micelles, whole cells (somatic cell-hybridization), membrane chemical methods like Ca $(PO_4)_2$ ligands have been used by Wigler *et al*. (1978). Physically, micro-injection can be applied and viral genome as vectors have been also used (Kotin *et al*., 1990; Zhang *et al*., 1993).

Pushing the Gene at the Desired Place on the Chromosome

It has been successfully applied in yeasts, not in mammals. An aberrant chromosomal location may interfere in its functioning. The most suitable method for this would be to achieve recombination of normal genes with the mutant ones in the homologus chromosomes, some genes have been seen shifting their position like transposons in the immune system and would be difficult to precise them. Biolistic transfer of DNA to target site is also possible (Lasalle, 1997; Klein *et al*., 1992; Sanford *et al*., 1991).

Activation of Alternative Genes Already Present in the Cell

An inactivated gene, not functioning to produce a protein, can be reactivated, a process known as demethylation. A cytidine analogue 5 AC (5-Azacytidine) replaces cytidine of DNA/RNA which normally caused methylation and inactivation of gene. This analogue can interfere with the methylation and hence can activate the gene. Arthur Nienhus of NTH, Bethesda (USA) and University of Illinois in Chicago, has treated B-thalassaemia by using this method. Gamma globulin is produced in fairly high amount in foetal life and with alpha-haemoglobin, it forms foetal-haemoglobin during foetal life. In adults gamma haemoglobin is not produced (due to gene being methylated), instead B-globin are produced, to make adult haemoglobin. In the case of B-thalassaemia B-globin synthesis is entirely absent due to mutant gene, causing anemia. In such patients, 5AC is found to induce gamma globin-synthesis once again by demethylation of the suppressed gene and with gamma-globin; this foetal haemoglobin, now produced, is adequate at least to meet the normal adult requirements of the patients.

ETHICAL STATUS

However, such human intervention in the scheme of Nature raises many ethical questions as many malpractices have crept in the name of research in the field, viz., injection of tumor cells into the body of uniformed patients, or even retarded children (Veatch, 1997). Great caution has been raised on moral action on the prevention and therapy of these disease, which may smack at times even of racism (Monagle, 1998). Yet the toll of death both in developing and developed countries make it inevitable to go for control as well as gene therapy of the diseases. Some broad guidelines for counseling and the responsibilities of counselor may be presented here, especially for the Indian sub-continent (Baker *et al*., 1998). According to Manorama Thomas (3), the following aspects should comprise essential components of counseling: give plenty of time for counseling, answer queries by the consult and have latest information on disease, possess good laboratory, use diaguostic aids like POSSUM, LONDON DYSMORPHIC DATABASE or SYNDROC, have diagnosis, karyotype, pedigrees to show to the patient (Counselling Aids for Geneticists, Greenwood Genetic Centre), compassionate, the information conveyed should be risk impact of disease on family, modification of the impact of risk, anticipated future development.

Some of the debates on ethics may be presented here:

Amniocentesis

The amniotic fluid from the womb is withdrawn through intravaginal or transabdominal route and the fluid is collected through a sterile catheter and taken into a test tube (Sutton, 1985). The cells are cultured and the karyotypes prepared, the abnormal karyotypes confirm the chromosomal disorders and the foetus is terminated by MTP. The law for amniocentesis exists but unfortunately, the normal female fetuses are also being aborted, resulting into dwindling female population. The alternative technique called Chrionic Villus Sampling (CVS) is safer, as it needs only four weeks of preguancy period and abortion is less traumatic. The ethical issues are here two-fold, the health of mother and the health of foetus which is more important. Anti-abortionist and foetal rights group have consternation

from feminists who give primacy to mothers. When does foetus acquire person-hood, a general consensus is the formation of primitive steak or development of nervous systems. Foetal medicine is still in infancy and therefore, ultrasonography, echolocation, echosounding and other techniques will better focus on the area.

The problem of genetic screening poses yet another problem (Levy and Alberts, 1998). What if prospective partners can be diagnosed for carrier-status, the suppressed or recessive genes of parents get expressed in the child if the child inherits both the recessive gene (1 in 4). This is preventive method to check the birth of such children either by preventing marriage or if married, checking all the fetuses. Now this poses a castigation upon the carriers who would be taken as some abnormal being and hence witchhunting can start. Complete confidentiality may not be possible. Complete confidentiality may not be possible and social problems can result (Fund, 1987; Roche and Annas, 2001).

With this is also related the problem of ethnic origin of some disease, like cystic fibrosis in Ashkenazi jews, the thalassemias among the Cypriots and Mediterreaneans and in India, amongst the Sindhis and Punjabis (125). Such screening is to be made compulsory for risk groups and can led to the notion of imperfect race and hence persecution by some zealots, in the name of cleaning the gene pool (Balgir, 2000).

The third measure for correction of genetic diseases is gene therapy (Anderson, 2003). Here the problem of clinical trial with informed consent is important. Even death has resulted due to the gene therapy protocol and some consent is important. Some animal models or primate trials have to be perfected before application among humans. Many types of cancer are waiting gene therapy in absence of proper trial. Suspicions are thus raised when developed countries undertake the trials in underdeveloped countries and the lure of petty money brings make-belief consent. The havoc can be imagined.

CONCLUSION

Much of human and medical genetics concerns the relationships that exist between human genes, the variation and mutations that occur within these genes and the phenotypes that results from these mutations. About 5000 human phenotypes have been documented in the ouline catalogue of mendalian inheritance in man. No more than 2000 human genes have been directly implicated in genetic disorders and single gene defects have an important role in various disorders causing enormous burden for patients, families and societies. Human genome science has initiated a new diagnostic tool of understanding the genetic disorders and bringing together computational and structural biology and bio informatics on a common platform and help in understanding new discipline like system biology to address public health problems.

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