Human Genetics

Introduction

In a restricted sense, “Heredity” has been used to refer to the inheritance of species and parental characteristics. In this sense it is the cause of similarities between the individuals. Obviously, this is the reason why brothers and sisters quite resemble with each other. Individual characteristics are different in different individuals and, hence, help in identifying one individual from all others, including his/her own real brothers and sisters. These are called “Variations”. Some of these may develop merely due to influences of food, temperature, habitat and other environmental factors. These are, therefore, called acquired or somatogenic characteristics. The other variations, called blastogenic characteristics, are genetic like species and parental characteristics, but these are due to inheritance of somewhat variable genetic material by different individuals.

Organisms regularly transmit characteristics from one to the next generation. This phenomenon is called “heredity” or “inheritance” and the characteristics so transmitted are called hereditary or genetic. “Heredity” is also sometimes defined as “Sum total of an individual's, inherited characteristics”, or “Tendency of an organism to develop in the likeness of its progenitors”. or “The genetic continuity between successive generations”.

The term Genetics (Gr., gen = to generate, or to become, or grow into) was introduced by **W. Bateson** (1905) for the “Branch of biology dealing with Heredity and Variations”, or say “Similarities and dissimilarities between organisms related by descent”. or simply “The study of heredity and hereditary variations.” Mendel was an Austrian monk who worked in 19th centuary.

14.1 Chromosomes

Chromosomes are Hereditary vehicle of Inheritance. Chromosome were first discovered by **Hofmeister** in the pollen mother cells of *Tradescantia* in 1848. In simple prokaryotic cells, it forms a single chromosome and lies in the cell cytoplasm. But in eukaryotic cells, DNA is contained in chromosomes which remain isolated from the cell cytoplasm and are enclosed in a nucleus. The chromosomes are capable of self–reproduction and maintaining morphological and physiological properties through successive generations. They are capable of transmitting the contained hereditary material to the next generation. Hence these are known as ‘**hereditary vehicles**’.

(i) **Chromosome theory of heredity :** The chromosome theory of inheritance was postulated by **Sutton** and **Boveri** independently in 1902. The salient features of this theory are as follows

(a) The somatic cells of an organism which are derived by the repeated divisions of the zygote are all diploid, i.e., these consist of two identical sets of chromosomes. One set of chromosomes is received from

mother (maternal set) through ovum and the other set is inherited from father through sperm (paternal set). These two chromosomes of one type constitute the homologous pair.

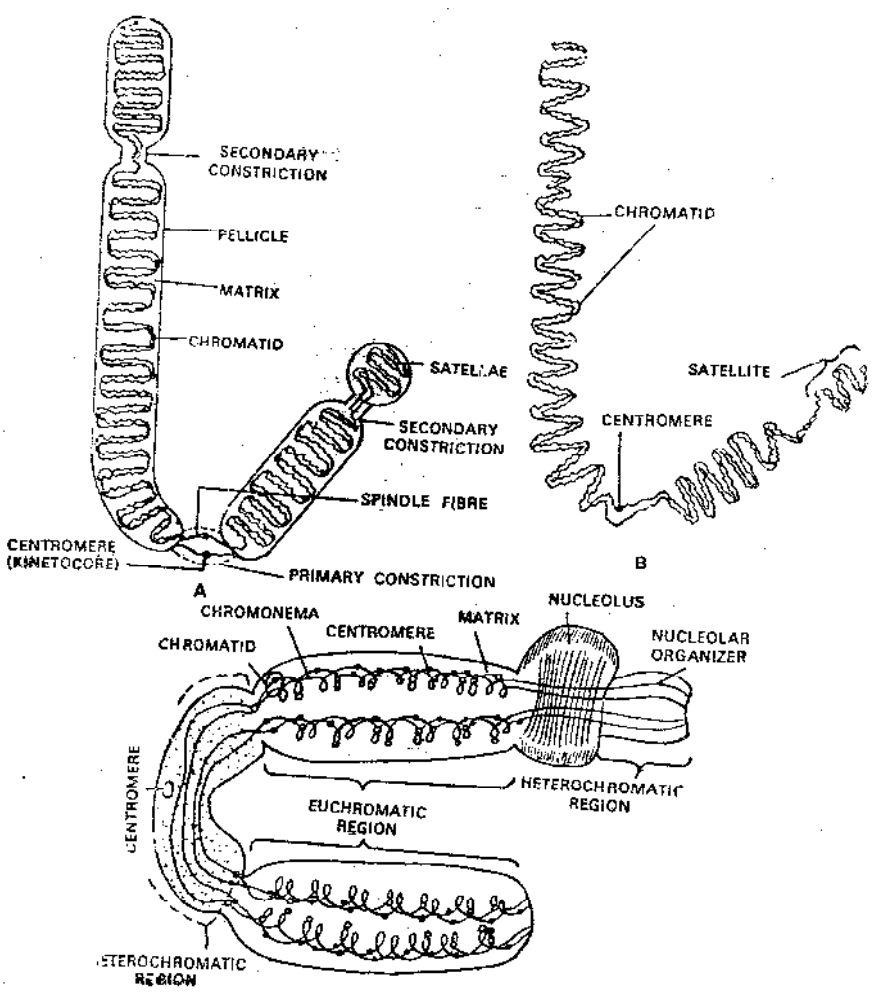
(b) The chromosomes retain their structural uniqueness, individuality and their continuity throughout the life–cycle of an organism.

(c) Each chromosome carries specific determiners or Mendelian factors and plays a significant role in the development of an organism from the zygote.

(d) The behaviour of chromosomes during meiosis, which occurs at the time of gamete formation provides an evidence that genes or determiners are located in the chromosomes. This also explains the mechanism of segregation of characteristics at the time of gamete formation.

(ii) **Eukaryotic chromosomes :** In resting nondividing eukaryotic cells the genome is nucleoprotein complex, called **chromatin**. It is amorphous and is randomly dispersed in the nuclear matrix as interwoven network of fine chromatin threads. When cell prepares to divide, the chromatin condenses into a species–specific number of well defined chromosomes.

(1) **Number :** The number of chromosomes in the somatic cells of higher animals and plants is known as diploid or somatic or zygotic number, while in the gametes (sperms and eggs) it is haploid, gametic or reduced. The number of chromosomes is constant in all the somatic cells of all the individuals of a species. Chromosome number is used in the identification of species and in tracing the relationship within the species. Highest number of chromosome in an animal is *Hydra vulgaris* (92) minimum number of chromosome in an animal is *Ascaris megalocephala* (2).



(A) and (B) Structure of typical somatic chromosome at anaphase of mitosis. (C) Schematic diagram of chromosome structure (Modified after Finean 1967)

(2) **Size :** The anaphase chromosomes range from $0.1\,\mu$ to $30\,\mu$ in length and $0.22\,\mu$ to $2\,\mu$ in width.

(3) **Shape :** The shape of chromosomes is usually determined by the type and the position of its centromere. Depending upon the position of centromere the chromosomes in anaphase may assume the form of rod, **J** or **V.**

(4) **Structure :** Different Regions Recognized in Chromosomes

Primary constriction and centromere : A part of the chromosome is marked by a constriction. It is comparatively narrow than the remaining chromosome. It is known as primary constriction. Its position is

constant for a given chromosome and forms a feature of identification. The primary constriction divides the chromosome into two arms. It shows a faintly positive Feulgen reaction, indicating presence of DNA of repetitive type. This DNA is called centromeric heterochromatin.

Secondary constriction or nucleolar organizer : Sometimes one or both the arms of a chromosome are marked by a constriction other than the primary constriction. During interphase this area is associated with the nucleolus and is found to participate in the formation of nucleolus. It is, therefore, known as nucleolar organizer region or the secondary constriction. Its location on the chromosome is marked with a lightly stained constricted region.

Nucleolar organizer region (NOR) : In certain chromosomes, the secondary constriction is intimately associated with the nucleolus during interphase. It contains genes coding for **18S** ribosomal RNA and is responsible for the formation of nucleouls. It is, therefore, known as nucleolar organizer region (NOR). Its location in the chromosome is marked by a lightly stained constricted area and is constant for a given chromosome. In man, the nucleolar organizers are located in the secondary constrictions of chromosomes 13, 14, 15, 20 and 22.

Tertiary constriction : The tertiary constrictions are present in nearly all the chromosomes. Their significance is not known. However, these help to distinguish one chromosome from others.

Telomeres : Telomere is the term applied to each end of a chromosome. The tips of the chromosomes are rounded and sealed and are called telomeres.

Satellite : The terminal part of a chromosome beyond secondary constriction is called satellite. The chromosome with satellite is known as SAT chromosome.

Chromatids : At metaphase stage a chromosme consists of two chromatids joined at the common centromere. In the beginning of anaphase when centromere divides, the two chromatids acquire independent centromere and each one changes into a chromosome.

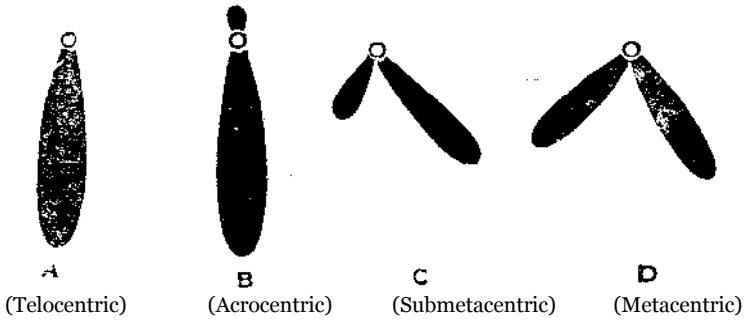
Pellicle : The outer most layer of chromosomes is called pellicle.

(5) **Location :** Centromere or kinetochore lies in the region of primary constriction. The microtubules of the chromosomal spindle fibres are attached to the centromere. Therefore, centromere is associated with the chromosomal movement during cell division.

(6) **Types of chromosomes based on position of centromere :** Based on the location of centromere the chromosomes are categorised as follows :

(a) **Telocentric** are rod–shaped chromosomes with centromere occupying a terminal position. One arm is very long and the other is absent.

(b) **Acrocentric** are rod–shaped chromosomes having subterminal centromere.



Types of chromosomes according to the position of centromere.

(c) **Submetacentric are J**–shaped chromosomes with centromere slightly away from the mid point so that the two arms are unequal.

(d) **Metacentric** are V–shaped chromosomes in which centromere lies in the middle of chromosome so that the two arms are almost equal.

(7) **Functions of centromere :** The centromere is considered to perform following two functions :

(a) Attachment of microtubules of chromosomal spindle fibres and help in chromosomal movement during cell division.

(b) The centromere serves as a nucleation centre for the polymerization of tubulin, the protein used in the formation of microtubules. It might help in the formation of microtubules. Thus it might help in the formation of spindle fibres during prometaphase and metaphase.

14.2 Molecular organisation of chromosome

According to Dupraw (1965–76) and Hans Ris (1976) each chromatid of eukaryotic chromosomes is formed of a single greatly elongated and highly folded fibre of DNA with its associated protein. This is known as unistranded or unineme concept. The chromatin is formed of about 60% proteins, 35% DNA and 5% RNA. The DNA in the largest chromosome of drosophila is about 4.0 cm long with a molecular weight 80×10^9. In chromosomes, the material controlling heredity is DNA. The DNA molecule of individual human chromosome ranges from 1.7 to 8.5 *cm* in length when uncoiled. The information stored in DNA is organized, replicated and read by a variety of DNA–binding proteins. These fall into two categories.

(i) **Structural proteins or packaging proteins :** These are non–specifically binding proteins. These are bound to DNA along most of its length and help to package it without preventing the access of other DNA–binding proteins.

(ii) **Histones :** Histones are main structural proteins found in eukaryotic cells. These are low molecular weight proteins with high proportion of positively charged amino–acids (basic amino acids–arginine and lysine). The positive charge helps histones to bind to DNA and play a crucial part in packing long DNA molecules. There are five different type of histones that fall into two categories.

(a) **Nucleosomal histones :** These are small proteins responsible for coiling DNA into nucleosome. These are H2A, H2B, H3 and H4. These form the inner core of nucleosome. Nucleosomal histones are very similar in different species (i.e., these have not changed during evolution). These are present in equimolar amounts, two of each type being present every 200 base pairs thus forming an histone octamer or core particle.

(b) **H1–histones :** These are large and are tissue specific. They are present once per 200 base pairs. These are loosely associated with DNA. H1 histones are responsible for packing or nucleosomes into 30 nm fibre. Nucleosome model is given by Kornberg and nucleosome term given by Oudet.

(iii) **Nucleosomes :** Nucleosomes are the fundamental packing units of chromatin and give chromatin the beads on a string appearance.

(a) **Core particle :** The core particle particle consists of the octamer of histones, having two copies each H2A, H2B, H3 and H4. It is about 11 nm in diameter and 6 nm in height. A strand of DNA having 146 base pairs is tightly wrapped around this core forming two circles.

(b) **Spacer DNA :** It is a small segment of DNA having just four base pairs. One unit of histone H1 is associated with it.

(iv) **Functions of histones :** Histones in eukaryotic chromosomes serve two functions –

(a) These either serve as structural elements and help in coiling and packing of long DNA molecules.

(b) These cover or repress specific segment of DNA, so that they are unable to transcribe. Their transcription is possible only by dissolution of histones in respones to certain molecular signals.

14.3 Special types of chromosomes

(i) **Lambrush chromosomes :** In the oocytic nuclei of those animals which have large yolky eggs, the prophase of first meiotic division is extremely extended. During this phase the oocyte grows and synthesizes nutrients for the future embryo. In them, the chromosomes become greatly enlarged and assume unusual configuration. A large number of loops project out from the chromatid axis, giving a lampbrush appearance. Hence, these chromosomes are called lampbrush chromosomes.

(a) **History :** Lampbrush chromosomes were first observed by Flemming (1882) in amphibian occyte. A detailed study was made by J. Ruckert (1892) in the oocytes of sharks.

(b) **Occurrence :** Lampbrush chromosomes are found in the oocytes of insects, sharks, amphibinas, reptiles and birds which produce large and yolky eggs. These have also been found in plants and invertebrates like *Saggita, Sepia* and *Echinaster*.

(c) **Size :** Lampbrush chromosomes are large enough to be seen under light microscope,. These may be as long as $1000\,\mu$ or more and about 20μ in width. In Salamander oocyte these may attain length of about $5{,}900\,\mu$.

(ii) **Polytene chromosomes**

(a) **Occurrence :** Polytene chromosomes were discovered by Balbiani (1881) in the salivary gland cells of *Chironomous* larve. Polytene chromosomes are special types of interphase chromosomes that are large and visible with the naked eye. These giant chromosomes are found in the cells of salivary glands of Drosphila and *Chironomous*, in the cells of fat bodies of larval stages of certain Diptera. These were first observed in the salivary glands of *Chironomous* and hence are called salivary gland chromosomes.

(b) **Nature :** Polytene chromosomes are multistranded being composed of a large number of chromonema. Their number has been estimated to be 1024 by Painter; 16000 by Bearmann. The polytene chromosomes are formed during early larval development when mitotic divisions come to end in these tissues but the DNA replication continues. DNA undergoes about 10 consecutive duplications producing 2^{10} copies of DNA fibres.

(iii) **Supernumerary chromosomes :** In certain plants and animals one or more additional chromosomes were observed in addition to the normal number. Such accessory chromosomes are very small and generally inert, being composed of heterochromatin. Normally, their presence in the nucleus does not affect the phenotype but if these are too many reduce the fertility and vigour.

14.4 Human karyotype

The normal diploid number of chromosomes in man is 46 (i.e. 23 pairs). The new technique developed by two plant cytologists, **Tizo** and **Levan** in 1956 enabled the human geneticists to ascertain the correct chromosome number. Allosomes (hetero–chromosomes or heterosomes) are related with sex determination.

Depending upon the position of centromere and relative length of two arms, human chromosomes are of three types metacentric, submetacentric and acrocentric. The photograph of chromosomes are artificially arranged in the order of descending length in seven groups as shown in the table below –

S. No.	Group	Size	Position of centromere	Idiogram number	Total number of chromosomes in diploid cell.
1.	A	Large	Metacentric or submetacentric	1, 2, 3	3 pairs
2.	B	Large	Submetacentric	4, 5	2 pairs
3.	C	Medium	Submetacentric	6, 7, 8, 9, 10, 11, 12, & X	7 pairs + 1 in male (7 pairs + 1 pair in female)

4.	D	Medium	Acrocentric	13, 14, 15	3 pairs
5.	E	Small	Metacentric or submetacentric	16, 17, 18	3 pairs
6.	F	Smallest	Metacentric	19, 20	2 pairs
7.	G	Small	Acrocentric	21, 22, Y	2 pairs + 1 in male (2 pairs in female)

(a) **Karyotype and Idiogram :** This sort of arrangement of chromosomes represents relative morphology of chromosomes, the karyotype. This helps in proper identification and numbering of chromosomes. Any gross morphological change or abnormality in the shape or size of any of the chromosomes is easily identified. The term idiogram is the diagrammatic representation of a karyotype, which may be based on measurements of chromosomes in several or many cells.

(b) **Significance of study of human chromosomes :** Study of human chromosomes has helped a lot in correlating various human diseases, malformation and deformities with the abnormalties in the number and structure of chromosomes. These abnormalities may be in the autosomes or sex–chromosomes. The chromosomal abnormalities are present in 4-5 out of every 1000 live births and in one out of every five spontaneous abortions.

14.5 Recognition of sex from interphase cells

Barr body technique (Lyon's Hypothesis) : In human beings, the sex can be identified by observing the nucleus of their resting cells (the interphase nucleus). In the interphase nucleus of cells in females a dark stained chromatin mass is observed on one side. This is known as sex–chromatin or Barr body (after the name of its discoverer Murray Barr, 1940).

In has been explained by Mary Lyon that in early embryogenesis one of the two X–chromosomes becomes genetically inert and forms the Barr body. This is known as Lyon's hypothesis. It means there is one Barr body in female and none in male or the number of Barr bodies is always one less the number of X–chromosomes. In cases of sex anomalies an abnormal male has one Barr body and an abnormal female (XO) does not show Barr body. In triploid males and females (XXX) or tetraploid males (XXXY) there are two Barr bodies.

S.No.	Particulars	Sex phenotype	Sex–chromosome	Number of bar bodies
1.	Normal Male	Male	XY	0
2.	Normal female	Female	XX	1
3.	Turner Syndrome	Female	XO	0
4.	Klinefelter Syndrome	Male	XXY	1
5.	Triple X–Syndrome	Female	XXX	2
6.	Triple X–Y Syndrome	Male	XXXY	2
7.	Tetra X–Syndrome	Female	XXXX	3
8.	Tetra X–Y Syndrome	Male	XXXXY	3

Some known chromosomal abnormalities

Karyotype	Common name of abnormality	Clinical symptoms
Trisomics		
1. Trisomy 13	–	Multiple defects, death by age of 1–3 months
2. Trisomy 15	–	Multiple defects; death by age of 1 to 3 months
3. Trisomy 18	–	Ears deformed, heart defects, spasticity and other damages; death by the age of 1 year
4. Trisomy 21	Down Syndrome	Earlier known as Mongolism; Oriental features. Epicanthus skin fold above the eye, mental retardation (I.Q. usually below 70); short stature, protruding furrowed tongue, transverse palmar crease; susceptible to

		respiratory infections and to leukemia.
5. Trisomy 22	–	Similar to Down syndrome but with more skeletal deformities.
6. XO	Turner's Syndrome (gonadial disgenesis)	Short stature, webbed neck. Females with poorly developed breasts and degenerated ovaries and rudimentary sexual characterstics, with slight mental retardation.
7 XXY	Klinefelter's Syndrome	Male with slowly degenerating testes, enlarged breasts.
8. XYY	–	Usually tall male, heavy acne of skin; Aggressive, and mild mental retardation.
9. XXX	Triplo–female	Despite triploid X–chromosomes, the female is usualy fertile and fairly normal.
Monosomics		
10. Deletion of short arm of chromosomes–5	Cri–du–chat syndrome	Microcephaly; severe mental retardation; in infancy cry resembles that of a cat.
11. Deletion of one arm of chromosome–21	Philadelphia chromosomes	Chronic granulocytic leukemia.

14.6 Anomalies of autosomes

(i) **Aneuploidy in man :** The autosomal aneuploids are produced by the nondisjunction between the chromosomes of any one of the 22 pairs of autosomes. The first autosomal abnormality was described under the name mongoloid idiocy or Down's syndrome. Certain commonly known aneuploids of man with monosomy and trisomy are as follow.

(a) **18–Trisomy :** Trisomy for 18th chromosome (of group E chromosome) causes severe deformities. This produces receding chin, malformed ears and defective nervous system. The helix of the ear is scarcely developed and the head is laterally compressed. The hands are short and show little development of second phalanx. Their digital imprints are simple. Such children usually do not survive beyond one year of age.

(b) **13–Trisomy or D–Trisomy (Patau's syndrome) :** The common anomalies of D–trisomy include here–lip, cleft–palate, sloping forehead with relatively small head and brain and defective eye development. The internal organs are severely malformed and patient often suffers from disorders of kidney and heart. Death usualy occurs soon after birth. About one out of 1000 new born babies exhibits trisomy.

(c) **21–Monosomy :** This is caused by the complete loss of one chromosome of the 21^{st} chromosome pair. Therefore, the patient has only 45 chromosomes instead of normal 46 and only one chromosome of the 21^{st} pair. This is lethal to the patient. However, partial loss or loss of its major part produces morphological features opposite to Down's syndrome. Their nose is prominent and distance between the eyes is less than normal, ears are large and muscles are contracted.

(d) **18–Monosomy :** This syndrome exhibits features opposite to those of the trisomy of 18^{th} chromosome. The ears are volumnous, the fingers are long and digital imprints are complex and convoluted. It has been described that about 40 percent of the aborted embryos in the first three months of pregnancy are presumed to possess trisomy or chromosomal error.

(ii) **Polyploidy in man :** Though very uncommon, a few cases of polyploidy have been observed in man. When chromosomes sets are present in multiples of n, the condition is called as euploidy. or polyploidy.

(a) **Monoploid (haploid) :** With only one set of chromosomes (n) or with a single genome. Genome refers to haploid set of chromosomes or total number of genes present on a haploid set of chromosomes.

(b) **Diploid (2*n*) :** The common chromosome number in the somatic cells of plants and animals.

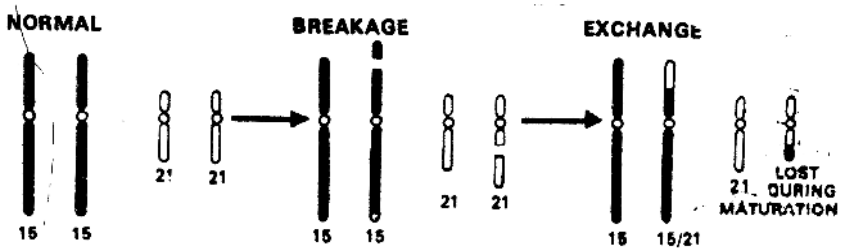
(c) **Polyploids :** Euploids with three or more complete sets of chromosomes are called polyploids. The term "polyploid" was introduced by Strasburger in 1910. The tapetal nuclei in anther of many angiosperm flowers are mostly polyploid. An example of triploid tissue is lilly endosperm and endosperm of wheat.

14.7 Structural chromosomal aberration in man

Structural aberrations of all kinds like translocation, deletion, duplication, ring chromosomes, inversion and isochromosomes have been observed in man and are found to be associated with abortion and various congenital diseases. Some of them are as follows

(i) **Translocation :** Translocation between chromosome 21 and either chromosome 14 or 15 has been observed in man. This also results in Down's syndrome or mongoloids. Such patients have 46 chromosomes with two normal 21 chromosomes and one unpaired large chromosomes which is formed by the fusion of the long arms of chromosomes 21 and 15. Therefore, in translocation or Down's syndrome the genetic material of chromosome 21 is present in triple dose and such cases are phenotypically indistinguishable from those with 21 trisomy.

The translocation mongolism runs in families and in such families the risk of a mongoloid child is one in three. Usually, the mother is a carrier of a balanced 21/15 translocation and phenotypically she is normal. but this translocation event is not confined to the mother only. Cases are known in which father has been the carrier.



Translocation between 21/15 chromosomes produces single large chromosome to produce Down's syndrome.

(ii) **Deletion :** The effect of loss of a portion of a particular chromosome depends on the particular genes lost. A deletion involving loss of large number of genes is incompatible with life.

(a) **Lejeune (1963)** has described the effect of loss of a portion of the no. 5 chromosome. The affected infant has a rounded, moon–like face and utter feeble, plaintive cries similar to the mewing of cat (cat cry syndrome or *cri du chat* syndrome). These children remain mentally and physically retarded.

(b) Deletion of a part of 21 chromosome produces leukemia, a cancerous malignancy arising in blood forming tissue. This was observed by **Peter Nowell & D.A. Hongrford (1960)** in Philadelphia and is commonly known as philadelphia chromosome syndrome.

(c) Deletion of some part of one X–chromosome has been found to produce some sex anomalies. The deletion of short arm produces clinical symptoms similar to the XO Turner's syndrome.

(d) Isochromosome of the long arm of X–chromosome also produces Turner's syndrome because the short arms are lost during isochromosome formation in 2nd meiotic division.

14.8 Recessive inherited disorders

Albinism can be taken as an example of recessive inherited disorder governed by a single pair of genes. Albino (latin, albus: meaning white) are devoid of pigment in the skin, hair and eyes. The skin is very light and

hair whitish yellow and eyes appear pinkish. Albinos have poor vision sensitive to sunlight and prone to skin cancer. One out of 20,000 individuals are albino.

Albinism results from a recessive mutant of the normal gene. It develops only when individual possesses both the genes in recessive condition received one from each parent. It means both the parents of an albino child are heterozygous for this pair of genes. The recessive disorders tend to appear only in the siblings, not in their parents. Off springs with recessive disorders arise more often from consanguineous unions than from marriages of unrelated persons. This is because close relatives share more of the same genes than persons from the population at large.

14.9 Lethal recessive inheritance

Sometimes, a recessive gene has such a drastic effect that the infant dies either still born or after the birth. Some such examples of lethal or fatal recessive genes are as under :

(i) **Congenital ichthyosis :** The disease is characterised by the cracking and separation of skin into large scaly sections. Infants having recessive phenotype are either aborted or are born premature.

(ii) **Infantile amaurotic idiocy** (Tay–Sach's disease) **:** The disease is because of a recessive gene. The children having double recessive genes appear normal and healthy at birth, but within six months the nerves of the brain and spinal cord exhibit marked signs of deterioration. By the age of one year child lies helplessly in his crib, later loses his sight and finally becomes paralyzed. The death occurs by the age of 3 or 4 years. The disease is more common in Jewish heritage.

(iii) **Cystis fibrosis :** It is the disease of pancreas. The pancreas secretes abnormally thick or viscid mucus material which collects in intestine and blocks digestion. One child in every thousand carries recessive genes for this disease. It is more common in caucasians.

(iv) **Infantile hypertrophic pyloric stenosis :** The disease of obstruction of intestine in the neonatal period (3–7th week after birth) is also known as infantile hypertrophy.

14.10 Dominant disorders

It shows that the affected person has atleast one affected parent. However, the normal children of affected parents, when marry normal persons have only normal offsprings. This is because the harmful gene is dominant and can express itself even in heterozygous condition. The affected heterozygous parent transmits defective dominant gene to 50 percent of the children. Some of the dominant defective characters in man are as follows.

(i) **Achondroplasia :** It is a form of dwarfs. The affected individuals are small and disproportionate with abnormally short arms and legs. Only 20% of these achondroplastic dwarfs are found to reach adulthood because most of them die in the first year.

(ii) **Tylosis :** The persons with tylosis have excessively thick skin on their palms and soles.

Genetic disorders

Disorder	Mode of inheritance	Clinical description	Comments
(1) Alkaptonuria	Autosomal recessive	Pigmentation of cartilage and fibrous tissue, with development of arthritis. Darkening of urine due to presence of homogentisic acid.	Deficiency of enzyme homogentstic acid dehydrogenase in the metabolic pathway of phenyl–alanine (an amino–acid).
(2) Childhood pseudo–hypertrophic muscular	X–linked recessive	Muscles swell, undergo fatty degeneration.	Also known as Duchenne–type muscular dystrophy. Rare in

dystrophy		Progressive muscular deterioration leads to confinement, then to death in early twenties. Symptoms develop in first three years.	females; heterozygous females may exhibit minimuscle functional defect.
(3) Cystic fibrosis	Autosomal recessive	High level of sweat electrolytes, pulmonary disease, cirrhosis of liver, pancreatic malfunction. No. spermatogenesis in males. Life expectancy 12-16 years. Common in persons of North European ancestry.	Rheumatic fever and polio–myelitis combined. Thick mucus interferes with lung clearance. Responsible for more death than diabetes.
(4) Haemophilia	X–linked recessive	Chronic bleeding	Even heterozygotes have some cloating factor deficiency
(5) Lesch–Nyhan syndrome	X–linked recessive	Slowly developing paralysis accompanied by mental deficiency and self–mutilation. Enzyme required for purine metabolism missing, leads to gout.	Caused by the deficiency of single enzyme. Half the cells of female heterozygous are enzyme deficient.
(6) Phenylketonuria (PKU)	Autosomal recessive	Deficiency of liver phenyl–alanine hydroxylase leads to a depression in the levels of other amino acids, mental deficiency.	Cause light colouring of skin and hair as phenylalanine fails to change into tyrosin.
(7) Red–green colour blindness (i) Deutan variety (ii) Protan variety	X–linked recessive	Unable to distinguish green colour due to the absence of green cone pigment.	Unable to distinguish red colour due to absence of red cone pigment.
(8) Sickle cell–anaemia	Autosomal recessive (incompletely dominant)	Abnormality of red blood cells caused by the presence of an inapropriate amino acid in the beta –chain of haemoglobin molecule. Causes extreme distortion of shape (sickling) which leads to the premature destruction of cell.	
(9) Tay–Sach's disease	Autosomal recessive	Caused due to the deficiency of hexose–aminidase–A. Blindness, paralysis and death in first few years of life in most cases.	Common among jews of Eastern European ancestry.
(10) Tyrosinase–negative oculo–cutaneous albinism (T–albinism)	Autosomal recessive	Absence of pigmentation due to functional absence of tyrosinase. Susceptibility to cancer.	
(11) Tyrosinase–positive oculo–cutaneous albinism	Autosomal recessive	Reduction of pigmentation due to malabsorption of tyrosine by body cells.	

14.11 Sex-linked inheritance

Sex–chromosomes (XX–XY chromosomes) are primarily concerned with the determination of sex but these do carry some genes for other body characters. Such body characters whose genes are located on the sex–chromosomes and follow sex during inheritance are known as sex–linked characters. The genes governing the sex–linked characters are called sex–linked genes and their mode of inheritance is described as sex–linked inheritance.

The genes located on the X–chromosome are called sex–linked genes or X–linked genes and genes present on Y–chromosome are described as holandric genes (G. holes, whole; andros, male), because they are present only in males. Certain characters are not sex–linked but are limited to one sex. These are described as sex–limited characters and sex–influenced characters. One of the earliest known instance of sex–linked character is the bleeding disease haemophilia observed only in males in the royal family of Spain. However, the concept of sex–linked inheritance was introduced by **Thomas H. Morgan** in 1910, while working on *Drosophila melanogaster*.

(a) The first attempt to show linkage in plants was done in *Lathyrus odoratus*.

(b) An exception to mendel's law is linkage.

(c) The number of linkage groups corrosponds to the haploid number of chromosomes.

(d) The transferase of genes from one chromosome to another during synapsis is termed as crossing over.

(e) Crossing over takes place at 4 strands stage between pachytene and diplotene.

(i) **Recessive sex linked inheritance in man :** The recessive X–linked genes have characteristics criss–cross inharitance, i.e., male transmits his X–linked recessive genes to his grandson through his daughter. A number of well known diseases and traits are caused by X–linked recessive genes. Approximately twenty characters of man exhibit sex–linked inheritance and their genes located on the X–chromosome. But the most popular examples of sex–linked inheritance are: (a) Red–green colour blindness, and (b) Hemophilia.

(a) **Red–green colour blindness :** Persons unable to distinguish certain colours are called colourblind. Several types of colour blindness are known but the most common one is 'red green colour blindness'. It has been described by Horner (1876). The red colour blindness is called protanopia and the green blindness deutoranopia. X–chromosome possesses a normal gene which controls the formation of colour sensitive cells in the retina. Its recessive allele fails to do its job properly and results in colour blindness. These alleles are present in X–chromosome is evidenced by the following results:

(1) When a normal woman is married to a colourblind man, all her sons and daughters have normal colour vision, but when her daughters are married to man with normal colour vision some colourblind sons are formed. It means that a woman with normal colour vision whose father is colourblind gives birth to children, of which about half of the sons are colourblind and other half are normal.

(2) If a colourblind woman is married to a normal man, all her sons are colourblind whereas all the daughters have normal colour vision. But when these daughters having normal colour visions are married to a colourblind man, the colourblind grandsons and grand–daughters are produced with almost equal number of normal grandsons and grand–daughters. It means that a colourblind woman has sons all colourblind and daughters all with normal vision and a colourblind woman always has a colourblind father and her mother is a carrier.

Inheritance of colourblindness

Parents				**Offsprings**			
Female		**Male**		**Daughters**		**Sons**	
Genotype	**Phenotype**	**Genotype**	**Phenotype**	**Genotype**	**Phenotype**	**Genotype**	**Phenotype**
1. XX	Normal	X^cY	Colour-blind	XX^c	Carrier	XY	Normal
2. XX^c	Carrier	XY	Normal	(i) XX (ii) XX^c	Normal Carrier	XY X^cY	Normal Colour–

							blind
3. XX^c	Carrier	X^cY	Colour-blind	(i) XX^c (ii) X^cX^c	Carrier Colour–blind	XY X^cY	Normal Colour–blind
4. X^cX^c	Colour–blind	XY	Normal	X^cX	Carrier	X^cY	Colour–blind

The above results could easily be explained with the assumption that colour vision is sex–linked character and its gene is present on the X–chromosome, Y–chromosome lacks its allele. In man sex–chromosomes, are XY, while in woman these are XX. It means that a man possesses only one gene for colour vision, whereas woman possesses two. The normal colour vision is dominant over colour blindness. Therefore, woman will be colourblind only when she has gene for colour blindness in both the X–chromosomes, whereas a man will be colourblind even when this gene is present singly. Always male receives its X–chromosome from mother (through ovum) and Y–chromosome from father (through sperm), whereas the female receives one X–chromosome from each parent (through ovum and sperm).

A woman whose all relatives have normal colour vision will naturally have gene for normal colour vision in both of its X–chromosomes (homozygous). If such a woman is married to a colourblind man, all her offsprings (sons as well as daughters) will have normal colour vision. From the above results following conclusions may be drawn:

(1) Colour blindness is more common in males than in females.

(2) Two recessive genes are needed for the expression of colour blindness in female, whereas only one gene gains expression in male.

(3) Males are never carriers.

(4) Colourblind women always have colourblind fathers and always produce colourblind sons.

(5) Colourblind women produce colourblind daughters only when their husbands are colourblind.

(6) Women with normal colour vision, whose fathers are colourblind, produce normal and colourblind sons in approximately equal proportion. A very rare autosomal genes causes total colour blindness

(b) **Haemophilia :** Bleeder's disease, haemophilia, in man is restricted entirely to male members. In haemophilic men the blood fails to clot when exposed to air and even a small skin injury results in continuous bleeding and can lead to death from loss of blood.

Haemophilia in females is very rare and it is obvious that it could not occur with same degree of severity as in man. A girl with severe bleeding would die by the time she reaches adolescence. The chance of homozygous girl being born in random mating is very slight, because the frequency of hemophilic males is about one in 10,000. Diabetes mellitus is also sex-linked disease.

(ii) **Dominant sex–linked genes in man :** The above discussed cases of sex–linked inheritance were concerned with the sex–linked recessive genes. There are some examples of dominant sex–linked genes. One dominant sex–linked gene produces defective enamel of the teeth and is found more frequently in women than in man because there are two X–chromosomes in women and only one in male.

14.12 Types of sex-linkage

The mechanism of sex–linkage is slightly different from the ordinary linkage of genes because the sex–linked genes are present on the sex chromosomes which do not possess homologous parts. Depending upon

whether the sex–linked genes are present on X or Y–chromosome, the sex–linked inheritance can be of the following types :

(i) **Digenic :** The sex–linked genes are present on the non–homologous part of X–chromosome and are passed on from male parent to male grandsons through daughters of F_1 generation. Naturally male sex is heterogametic.

(ii) **Diandric :** In this case the 2X–chromosomes of female behave as if these are completely homologous and female passes its one X received from female to male.

(iii) **Hologenic :** Character is directly passed from male to female.

(iv) **Holandric :** Genes which are in the non homologous part of Y–chromosome are passed on directly from father to son.

14.13 Sex-limited genes

Sex–limited genes are present in the autosomes but their expression is determined by the presence or absence of one of the sex–hormones. Therefore, these express themselves only in one sex. These differ from the sex–linked genes, which are actually located in the sex chromosomes. The sex–limited genes control the expression of primary and secondary sexual characters. They express their effects in only one sex and their action is clearly related to the sex–hormones. For example, beard–development in human beings is a sex–limited character. The genes for deep male voice and male musculature are expressed only in the presence of male sex–hormone. Similarly, genes for feminine voice, development of breast and feminine musculature are sex–limited characters. The abnormalities in hormone secretion may result in the development of breast in male or beard in female (hormone imbalance)

14.14 Sex-influenced genes

The sex–influenced genes are present in the autosomes whose dominance is influenced by the sex of the bearer. These are expressed more frequently in one sex than in the other. For example, pattern of baldness is dominant in man and recessive in female. This is because the gene for baldness (B) in heterozygous state (Bb) expresses itself in male but not in female. It means gene B for baldness behaves as a dominant in male and as a recessive in female. Horns in sheep and spotting in cattle are sex–influenced characters.

Genotype	Male	Female
BB	Bald	Bald
Bb	Bald	Not bald
bb	Not bald	Not bald

14.15 Dosage compensation

In Drosophila, large portions of X–chromosome remain euchromatic (turned on) in both males and females. The remaining portions appear to be a mixture of constitutive and facultative heterochromatin. A physiological effect analogous to facultative heterochromatization is observed in Drosophila. It ensures the same activities of sex–linked enzymes in both the sexes, even though the sex–linked genes are present in single dosage in males and in double dosage in female. This is accomplished.

(i) By facultative heterochromatization of one of the two X–chromosomes in females (Lyonisation).

(ii) By stimulated rate of gene transcription from the single male X–chromosome.

This is known as dosage compensation. Therefore, dosage compensation is the mechanism by which the effective dosage of X–linked genes in two sexes is made equal or nearly equal, so that the X–linked genes produced the same phenotypic effect in single or double dose.

14.16 Sex-determination

Sexuality : Biologically, sex is an aggregate of those morphological, physiological and behavioural qualities that differentiate the organisms producing eggs from those organisms producing sperm. The organisms producing eggs are known as female and those producing sperm are males. The sex behaves as a Mendelian character. Its inheritance follows law of segregation. The various genetically controlled sex–determination mechanisms have been classified into following categories.

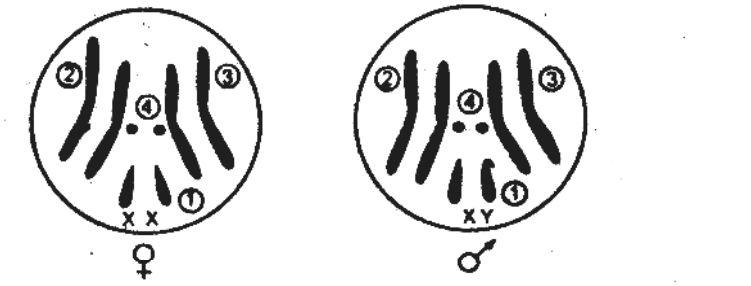
(i) Chromosome mechanism

(ii) Male haploidy or Haplo–diploidy mechanism

(iii) Genic balance mechanism

(i) **Chromosome theory of sex–determination :** In majority of diploid sexual animals are found a pair of sex–chromosomes which are specialized for sex–determination. These are represented by X and Y.

Sex–chromosomes and autosomes : The X–chromosome was first observed by German biologist, *Henking* in 1891 during the spermatogenesis in male bug and was described as X–body. The chromosome theory of sex–determination was worked out by E.B. **Wilson** and **Stevens** (1902–1905). They named the X and Y chromosomes as sex–chromosomes or allosomes and other chromosomes of the cell as autosomes.



Chromosomes of *Drosophila*. Note the three pairs of autosomes, which are similar in both the sexes and XX or XY are sex-chromosomes similar in female but dissimilar in male.

Sex–chromosomes carry genes for sex. **X–chromosome** carries female determining genes and Y–chromosome has male determining genes. The number of X and Y chromosomes determines the female or male sex of the individual. Autosomes carry genes for the somatic characters. These do not have any relation with the sex.

(ii) **Types of chromosomal mechanisms of sex–determination**

(a) **XX–XY type or Lygaeus type :** XX–XY type of sex–determining mechanism was first studied in the milk weed bug, *Lygaeus turcicus* by Wilson and Stevens. Therefore, it is called Lygaeus type. There are two different patterns of sex deter mination in Lygaeus type.

(1) **Female homogametic XX and male heterogametic XY :** The homogametic sex (XX) is female and produces ova all of one type, i.e., having X–chromosome. The male is heterogametic – XY and produces sperm of two types, 50% of which possess X–chromosome and other 50% Y–chromosome. This is simple XX–XY type and is found in man, drosophila and certain insects.

Example : In drosophila total number of chromosomes is eight, of which six are autosomes, common to both male and female. The fourth pair is of sex chromosomes. In male this is represented by XY (i.e., karyotype of male Drosophila 6 + XY and in female XX i.e., 6 + XX. Ova produced by female are all similar possessing 3 + X chromosomes, whereas the sperm produced by male are 3 + X and 3 + Y in equal numbers.

	X	X
X	XX	XX
Y	XY	XY

XX– female – 50%
XY–male –50%

Example : In case of man total number of chromosomes is 23 pairs or 46.

In male (man) 44 + XY

In female (woman) 44 + XX

The sperm produced by male are of two types (i) 22 + X, (ii) 22 + Y, whereas the ova all have 22 + X chromosomes.

(2) **Female heterogametic and male homogametic :** In fowl, other birds and some fishes, certain moths and butterflies, the female sex is heterogametic, with X and Y–chromosomes often represented by Z and W and laying two types of eggs, one half with X or Z chromosome and the other half with Y or W chromosome. The male sex is homogametic having XX or ZZ chromosomes. It produces sperm all of one type.

XX– XO type or Protenor type : McCLUNG in male squash bug (Anasa) observed 10 pairs of chromosomes and an unpaired chromosome. Their females have eleven pairs of chromosomes (22). Thus all the eggs carry a set of eleven chromosomes but the sperm are of the two types : fifty percent with eleven chromosomes and the other fifty percent with ten chromosomes. The accessory chromosome was X–chromosomes. Fertilization of an egg by a sperm carrying eleven chromosomes results in a female, while its fertilization by a sperm with ten chromosomes produces male. It is said to be evolved by the loss of Y–chromosome.

Example : Squash bug (Anasa)

Female: 22 chromosomes – 20 + XX → 10 + X, 10 + X

Male: 21 chromosomes – 20 + X → 10 + X, 10

The XO method is found in Orthopterans and Heteropterans.

(ii) **Female diploid and male haploid or hymenopteran type :** In honeybee, wasp, ants and certain other hymenopterans parthenogenesis is widespread. There are three types of individuals.

(a) **Diploid queens :** These develop from fertilized eggs and are fully developed functional females.

(b) **Diploid workers :** These also develop from fertilized eggs but are under–developed non–functional females, which are unable to produce ova.

(c) **Haploid drones or males :** These develop parthenogenetically from the haploid unfertilized eggs and are functional males.

In some species a bisexual generation from unfertilized eggs alternates with a female generation from fertilized eggs. There are certain forms where males are altogether absent and females are produced by parthenogenesis. These females are always diploid.

Different types of chromosomal mechanisms of sex–determination in animals

S.No.	Organism	Heterogametic sex	Gametes		Zygotes	
			Sperms	Eggs	Females	Males

1.	Drosophila, man etc.	Male	X and Y	All X	XX	XY
2.	Protenor (bug), grasshopper	Male	X and O	XX	XX	XO
3.	Birds, moths	Female	All X	X and Y	XY	XX
4.	Fumea (a moth)	Female	All X	X and O	X	XX

(iii) **Genic balnce theory :** Based upon the observations of ratio theory BRIDGES put forward genic balance theory in which he suggested that every individual whether male or female possesses in its genotype genes for both male and female characteristics. Which sex will actually develop is decided by the preponderance of that type of genes. If there is excess of female determining genes a female develops or if the ratio of male determining genes exceeds that of female determining genes a male is formed. The sex–chromosomes and autosomes are more vehicles of genes. In Drosophila the X–chromosome carries more genes that incline the development towards femaleness and the autosomes possess genes which incline the development towards maleness. Therefore, the deciding factor is the ratio between the number of X–chromosomes to autosomes. In Drosophila, following table represents the results of different ratios of X–chromosomes to the sets of autosomes.

Showing ratio of X and A chromosomes

S.No.	Sex	Number of X–chromosome	Sets of autosomes	Sex–index Ratio (X–A)
1.	Super female	XXX	AA	1.5 Super female
2.	Normal female — Tetraploid	XXXX	AAAA	1.0
	Normal female — Triploid	XXX	AAA	1.0
	Normal female — Diploid	XX	AA	1.0
3.	Intersex	XX	AAA	.66
		XXX	AAAA	.75
4.	Normal male	X	AA	.50
5.	Supermale	X	AAA	.33

14.17 Sex-differentiation

(ii) **Hormone and sex–differentiation :** The sex determination theories of chromosomes and genic balance successfully apply to the lower animals but in higher vertebrates and under certain conditions in invertebrates, the embryo develops some characters of the opposite sex together with the characters of its own sex–chromosome. It means, the sex changes under specific circumstances. This is due to the hormones secreted by the gonads of that animal. The theory is based upon the observations of CREW in chicks. He found that a hen which laid fertile eggs, accidentally lost its ovary, stopped laying eggs, and developed male comb, male plumage and became a cock. It finally functioned as male and became father of two chickens.

There are several examples of hormonal control of sex–differentiation. Some are discussed as under :

(a) **Sex–reversal :** The above case of sex–reversal was explained by assuming that as soon as the ovary was removed or destroyed the ovarian hormones were stopped and after sometime the dormant testes present as rudiments in almost all the female birds started functioning. The male hormones were produced and resulted in the appearance of male secondary sexual characters and the formation of sperm. Cases of sex reversal have been observed in fishes, amphibians, birds and even in mammals. The artificial removal of gonads of either sex before puberty in mammals and even in man, results in the development of secondary sexual characters of the opposite sex. The female characters can be induced in a castrated male by injecting

female hormone and vice versa. Cases of sex reversal in man have been found due to the irregularities in the functioning of adrenal and pituitary.

(b) **Free martinism :** Another example of early influence of hormones on sex determination comes from free martins often found in cattles. Lillie and others found that where twins of opposite sex (one male and other female) are born, the male is normal but female is sterile with many male characteristics. Such sterile females are known as free martins. The scientific explanation for the formation of free martins is the effect of hormones of the male sex on the female. In cattle the foetal membranes of the twins are fused in such a manner that they have a common circulation of blood. The female hormone is produced at a slightly later stage in the development and guides its development towards female side. But since the twins have a common circulation and blood passes from one twin into the body of other twin, the male hormone, which is produced slightly in advance of female hormone, enters the body of female twin and before the female hormone onsets the development of female characteristics it is already differentiated in the guidance of male hormone. As a result the developing female is sterile.

(c) **Intersexes :** Classical work of Goldschmidt on diploid intersexes in gypsy moth, *Lymantria* offers an important contribution towards understanding the mechanism of sex determination. *Lyamantria* extends from England to Japan and exhibits striking sexual dimorphism. While working on *Lymantria* Goldschmidt observed the following facts.

When *Lymantria dispar* (European race) males are crossed with normal, L. *japonica* females, the males and females of the progeny are all normal, but when the sexes were changed, i.e., when females of dispar of European race were crossed with males of japonica race the females were all intersexes, whereas males were all normal.

The mechanism by which intersexes develop is briefed by Goldschmidt. The intersexes start development as females or males in the guidance of their chromosomal configuration and develop as such upto a certain critical point or turning point, after which their development is switched on towards the opposite sex due to the appearance of hormones, which direct the development towards that direction. He has postulated certain hypothetical enzymes termed as and rase for initiation of maleness and gynase for femaleness. But experimental evidences in this connection are lacking.

14.18 Eugenics, Euthenic and Euphenics

Galton (1983) coined the term eugenics which, he defined in 1904 as “the study of agencies under social control that may improve or impair the racial qualities of future generations either physically or mentally” or “the branch of biology which deals with the application of the laws of genetics for the improvement of the human race”. The word eugenics is derived from Greek word, eugenics meaning “well born” and so itself express its objective. Jennings said “**Goodmen and Wisemen** will make a good world”.

(i) **Aims and ideals of eugenics :** Practically, every person will agree that mankind is away from perfect. Both, physically as well as mentally, there is a great need of improvement. The following will be the important things in which the improvement in human population can be speculated.

(a) **Health :** Robust health in physical and mental state is a desirable factor of the society and it can be preserved only by mean of eugenics.

(b) **Intelligence :** In the world of science, ability to think and reason straight is one of the most adaptive qualities in man. A reasonably high level of intelligence in an average man, plus superior ability in numerous individuals, is essential for the maintenance of high state of civilization.

(c) **Moral characters :** The word moral used for those qualities of the individual that express themselves by word or deed in all ways that tend to promote the good of the species. Consistent moral behaviour grows out of sympathy or fellow–feeling. In a species with a history such as ours moral behaviour can hardly exist without this friendly emotions. After doing good to a fellow man, a kind of satisfaction is felt.

(d) **Variability :** Specialization by different people in different fields of life is an essential feature of human progress. The special talents have a strong hereditary basis. In order to promote the general welfare, the state should encourage the multiplication of talented individuals.

If the foregoing premises are accepted the conclusion seems to follow that moral characters based upon intelligence and fellow feeling is highest ideal that we can have for man, because with such a character man has the means for endless progress towards perfection.

(ii) **Eugenics and Euthenics :** There are two fundamental methods that bring about the betterment in human populations.

(a) By improving the individuals after birth (Euthenics).

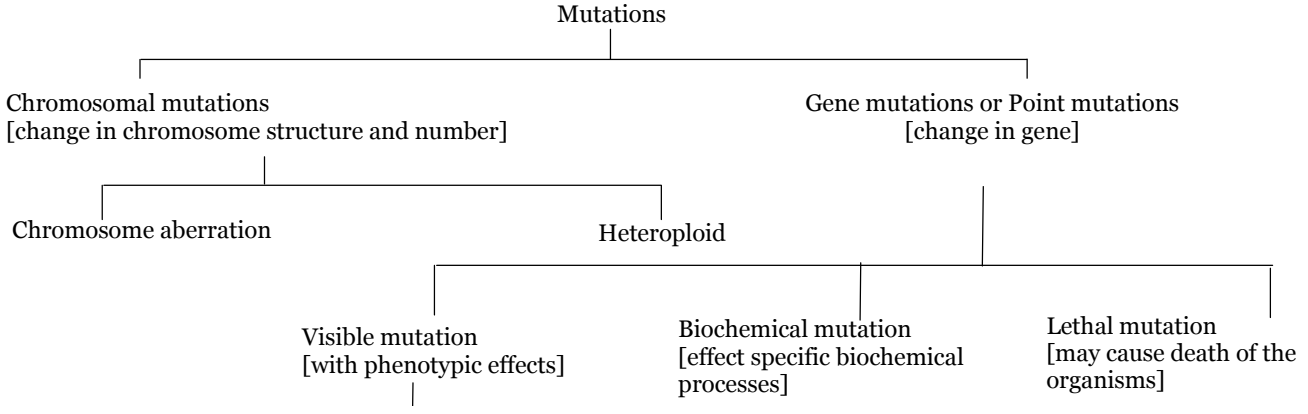
(b) By improving the race before birth (Eugenics).

In the first case, the qualities present in the individuals are developed by the most favourable environment and with the help of education. This is called euthenics or "**the science of learning to live well**." The second method consist in improving the genetic constitution of the future progeny by means of selective marriages and thus it was termed as eugenics, which is generally spoken as "the science of being well–born".

(iii) **Euphenic :** The symptomatic treatment of genetic diseases of man is called euphenics. Branch dealing with genetic engineering is euphenics. It deals with the control of inherited diseases, especially the inborn errors in metabolism in which the missing or defective enzyme has been identified. Such types of metabolic disorders are caused due to some defect in the genotype which fails to produce one of the specific enzymes required in the metabolism of a specific substance. One example of this type is the condition, known phenylketonuria (PKU) and another example **alcaptonuria, (ACU)** determined by the autosomal recessive gene.

14.19 Types of mutation

Hugo de Vries, (1901) experiments on the evening primrose, *Oenothera lamarckiana*, he brought into general usage the term mutation. Mutations are mainly responsible for variation in organisms. Mutation are rarely useful. A sudden and discontinuous changes in a gene, occuring rarely in any particular gene, and capable of producing a change great or small in some part of the body. It can also be defined as an event that gives rise to a inheritable alteration in the genotype. Scientific study on mutation started in 1910 when Morgan worked on *Drosophila melanogaster*, The gene is composed of deoxyribose nucleic acid (DNA). It influencs the phenotype of the individual and it is capable of change (mutation). (The smallest amount of DNA which is effective in causing a mutation is called the muton. Thus the muton is a micro–structure of gene that mutates.



(i) **Size based mutations**

(a) **Point mutation :** A change in a very small segment of DNA; usually considered to involve a single nucleotide or nucleotide pair.

(b) **Gross mutation :** A change involving more than one nucleotide pair; may involve the entire gene, the entire chromosome or sets of chromosomes (polyploidy).

(ii) **Origin based mutations**

(a) **Spontaneous mutation :** Often called "background mutation"; origin is unknown.

(b) **Genetic control :** The mutability of some genes is known to be influenced by other 'mutator genes'.

(1) **Specific mutations :** Effects limited to one locus.

(2) **Non-specific mutations :** Simultaneously affect many loci.

(c) **Induced mutations :** Through exposure to abnormal environments such as :

(1) **Ionizing radiation :** Change in chemical valency through the ejection of electrons are produced by protons, neutrons or by alpha, beta, gamma or X–rays.

(2) **Non-ionizing radiations :** Raise the energy levels of the atoms, rendering them less stable.

(3) **Chemical mutagens :** Are chemical substances which increase the mutability of genes.

Copy errors mutants arising during DNA replication.

Direct gene change produced in non-replicating DNA.

(iii) **Quality based mutations**

(a) **Structural mutations :** Changes in the nucleotide constant of the gene.

(1) **Deletion mutation :** Loss of some portion of a chromosome.

(2) **Insertion mutation :** Addition of one more extra nucleotides to a gene.

(3) **Substitution mutation :** Substitution of one nucleotide for another. Transition mutation substitutes one purine for another or one pyrimidine for another. Transversion mutation substitutes a purine for a pyrimidine or vice versa.

(b) **Rearrangement mutations :** Changing the location of a gene within the genome: often leads to "position effects".

(1) **Within a gene :** Two mutations within the same functional gene can produced different effects, depending on whether they occur in the *cis*–or *trans* position.

(2) **Number of genes per chromosome :** Different phenotypic effects can be produced if the numbers of gene replicates are non–equivalent on the homologous chromosomes.

(3) **Movement of gene locus :** Moving the gene locus may create new phenotypes. Translocations is movement of a non–homologous chromosome. Inversions is movement within the same chromosome.

Causes of mutations

(a) There is no doubt that in some of the cases, mutations are induced by natural radiations are eminating from radioactive substances in the rocks, soil, water or atmosphere on the earth from the body of the organism itself or from ultraviolet rays and cosmic rays arriving from outer space. All organisms on earth are exposed to such radiations. Calculations made by Muller and others, (1948) however, showed that the measured intensity of natural radiation is wholly inadequate to account for the observed rate or natural mutations in Drosophila.

(b) Some natural or spontaneous mutations are due to the chemical environment, including those chemical substances, which usually come along with food.

(c) It has further been noted that the rate of spontaneous mutation is increased with the rise of temperature.

(d) It is also possible that a change in the gene may occur as an accidental result of metabolism of the cells, perhaps through the occasional failure of the gene to duplicate itself with perfect accuracy during cell division, such change or slip would be expected more often at higher temperature.

(e) Mutations may also be due to the change in the sequence of purine pyrimidine pairs within a DNA molecule.

(f) Mutations could also occur by other means as well. For example, if at a given point in the sequence of nucleotide pairs, a pair is deleted or added, the result shall be a change in the sequence.

(g) Another way by which the mutations may occur would be through the insection of some foreign or unnatural base into the DNA whose pairing properties would be different from the natural base.

Benzer (1949) thus recognised the mutation as intragenic changes effect in a segment of five nucleotide of the DNA chain. **Bantley Glass** (1952) writes. “with no doubt; the analysis of the nature of the mutation will continue to provocative and will eventually be clarified in terms of the basic structure and organisation of the genetic material. Yet it is impossible at present to be sure whether mutations studied by genetists ever descend to the level of simple alteration in nucleotide or molecular structure.”

14.20 Tissue culture

Reverdin 1870 transplanted a very small piece of skin and performed the tissue implantation for the first time This technique is now employed for the production of some compounds used clinically as well as those employed for commercial use. In vitro production of insulin and the enzyme β–galactosidase; and the synthesis of monoclonal antibodies together with raising of clones of artificial genes are based on tissue culture technique. This is highly significant because this will avoid the elimination or danger of disappearance of the natural sources in the coming years. The main technique involved in agricultural biotechnology is called tissue culture. Plant tissue culture techniques have been successfully used for producing **shikonin**. Tissue transplantation can be classified into four types on the basis of genetic relationship between the donar and the recipient.

(i) **Isograft or isotransplant :** Transplantation between two twins (identical).

(ii) **Allograft :** Grafting between two members of the same species. This transplantation may be successful or may be rejected by the recipient.

(iii) **Autograft :** Donor and recipient of grafting is the same person. The rejection of transplantation is not possible.

(iv) **Xenograft :** Transplantation of tissue between two different species. Such transplantation is rarely successful.

14.21 Genetic engineering

The branch of biology by which important and permanent changes are created in plants and animals by increasing, decreasing, manipulation and transplantation of genetic units is called genetic engineering.

(i) **Aims of genetic engineering**

(a) The main aim of genetic engineering is to transplant the disturbed (nucleotide) chain by general nucleotide chain. These genetic disturbances are produced due to wrong nucleotide sequence or chain or by natural factors. Such genetic disturbances result many serious diseases like sickle cell anaemia.

(b) Altering the phenotype of an organism according to will by adding, removing or repairing of a part of genetic material is the main aim of genetic engineering. It is also called as biotechnology gene therapy, gene manipulation, gene transplantation.

(ii) **Techniques of genetic engineering :** Genetic engineering consists of two main steps :

(a) Isolation and study of the properties of desired genetic material, through which changes are created in the structure and functions of genes.

(b) Discovery of chromosome less genetic material known as vector (Carrier of genetic units) molecules such as plasmids, cosmids, lamda phase viruses. The techniques of isolation and purification of DNA have been successfully developed. **H.G. Khorana** (1968) has already described the artificial synthesis of gene of a known sequence of nucleotides. Thus by the process of genetic engineering chemical synthesis, transplantation in heterogenous DNA, transduction, auto-production and observation of polynucleotide chain is possible.

(iii) **Recombinant DNA Technology :** Recombinant DNA is the DNA formed by combining DNA from two different organisms. It is also called heterogenous DNA. Recombinant DNA technology involves the transfer of specific genes (segments of DNA) from one organism to the other by using restriction endonuclease enzyme and appropriate vectors.

Campbell was the first scientist who has described the process of gene manipulation by recombinant DNA technique after the manipulation of plasmid DNA in the bacterial DNA.

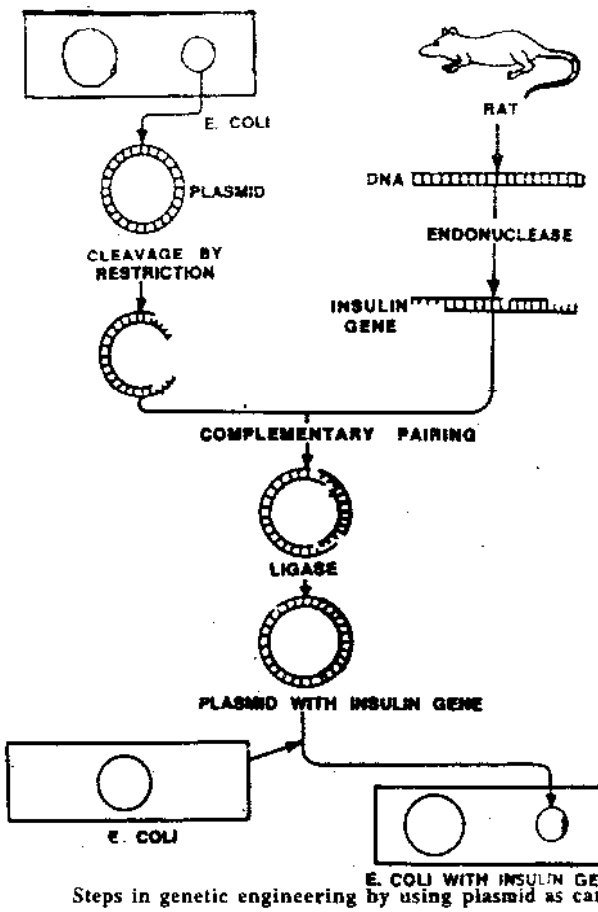
(iv) **Tools of Recombinant DNA Technology :** The following tools are required for recombinant DNA technology :

(a) **Foreign DNA :** The DNA segment to be transported from one organism by vector molecule is called as foreign DNA. It can be of following types:

(1) **Complementary DNA (c–DNA) :** DNA which is synthesized on m–RNA template with the help of enzyme reverse transcriptase is called **c–DNA**. The DNA strand formed in this way is than isolated from RNA–DNA complex. This isolated DNA strand synthesize its complementary strand by enzyme **DNA–polymerase** and becomes double stranded.

(2) **Synthetic DNA (s–DNA) :** It is artificially synthesized in the laboratory from free nucleotide triphosphates with the help of DNA–polymerase on DNA–template or without a template. **Khorana** and his associates (1965) produced first: DNA of **E.coli.**

(3) **Random DNA :** It is the entire DNA (with chromosome) of an organism which is broken into small fragments with the help of restriction endonuclease enzymes.



Steps in genetic engineering by using plasmid as carrier of genes

(b) **Enzymes :** Recombinant DNA technology involves the following types of specific enzymes :

(1) **Lysing enzymes :** Enzymes which are used to open the cells or dissolve the cell wall are called lysing enzymes e.g., Lysozymes. It is used to dissolve bacterial cell wall.

(2) **Cleaving enzymes :** These enzymes are used for the cleavage of DNA molecules. Three types of cleaving enzymes are known :

Exonucleases : These enzymes cut off nucleotides from 5′ or 3′ ends of DNA molecule.

Endonucleases : These enzymes cut off DNA molecule at any point but not at the ends.

Restriction endonucleases : These enzymes cleaves DNA fragment of a chromosome into smaller DNA fragment, bearing one or few genes at specific points called the recognition sites having palindromic sequences, **Palindromes** are base pair sequences that read the same forward or backward such as the word MADAM. *e.g* **:** Restriction endonuclease enzyme. (Eco R.I.) present in *E. coli*. It cuts the double stranded DNA at the point having *palindromic sequences* such as :

$$\begin{array}{c} G\ A\ A\ T\ T\ C \\ |||\ ||\ ||\ ||\ ||\ ||| \\ C\ T\ T\ A\ A\ G \end{array}$$

A large number of restriction endonucleases are now available commercially from several bacteria each of which recognises specific nucleotide sequence for cutting DNA into smaller fragments. So we can say that these enzymes act as **chemical scissors**. Restriction endonuclease enzymes are discovered by **Smith** and **Nathan** (1970). Restriction endonuclease enzyme found in bacteria also protects them against the entry of foreign DNA (viral).

(3) **Synthesizing enzymes :** These enzymes help in the synthesis of DNA, e.g., DNA polymerases, Reverse transcriptases. DNA–polymerases help in the synthesis of complementary DNA strands on DNA

template where as reverse transcriptase enzyme helps in the synthesis of complimentary DNA strands on RNA template.

(4) **Ligases :** These enzymes join or seal the gap present between DNA fragments, e.g., DNA–ligase.

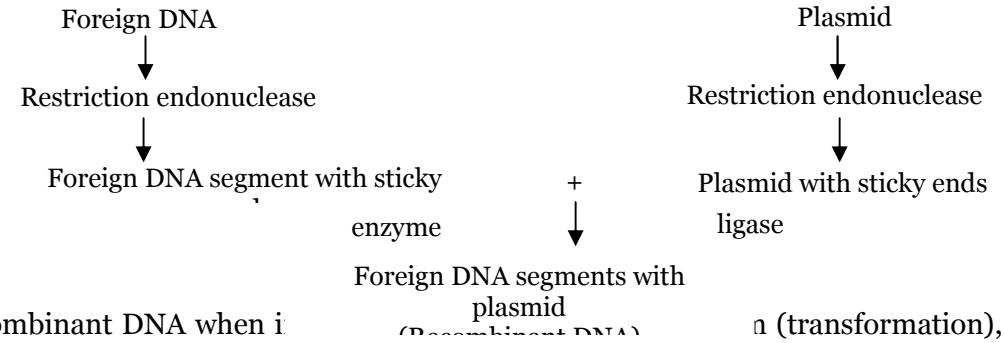
(5) **Alkaline phosphateses :** These enzymes act. on phosphate group from 5′ end of DNA strand.

(c) **Vector DNA Molecule :** The DNA which is used as transporter or carrier for transferring desired foreign DNA fragment into suitable host is called as vector DNA, e.g., Plasmid DNA, Lamda phase, Cosmids.

(i) **Mechanism of Recombinant DNA Technology :** Mechanism of recombinant DNA technology involves the following steps.

(a) **Isolation of desired gene or functional DNA segment :** From the eukaryotic cell desired DNA segment is isolated with the help of enzyme restriction endonuclease. Now this segment of DNA is known as foreign DNA.

(b) **Transfer of DNA segment from one organism to other :** Plasmid is an extra chromosomal circular DNA found mostly in bacteria over and above the main genome. When bacteria multiplies the plasmid DNA also multiplies along with the chromosomal DNA. These plasmids can be easily isolated from the bacterial cell with the help of restriction endonucleases. Plasmid serves as a vector for transferring the foreign DNA into a suitable recipient. Foreign DNA and plasmid sliced with the help of endonucleases has free sticky ends through which they join each other with complementary base pairing with the help of enzyme ligase. Thus a recombinant DNA is formed.



Such a recombinant DNA when i n (transformation), it replicates and expresses itself. Within the bacterial cell the recombinant DNA molecule replicates along with the endogenous DNA of the host cell and produces copies of cloned DNA. This process is known as **gene cloning**. The cloned recombinant DNA produced in large quantities can be isolated, purified and analyzed. Plasmids are ring of DNA occuring in bacteria additional to main genome. Plasmids are without vital genes but carry genes for sexuality, antibiotic resistance etc. Restriction endonuclease is used to cut the plasmid as well as the foreign DNA molecules at specific paints. Transduction is the transfer the bacterial genetic material from one bacterium to another using a phage as the vector.

(v) **Application of genetic engineering in medical field**

(a) The hereditary diseases like colour blindness, haemophilia which, are caused by recessive genes; and also many inborn metabolic disorders due to defective genes as alkaptonuria, phenylketonuria can be cured with the gene therapy.

(b) Substances like vitamins, hormones, amino acids and antibodies can be synthesized in bacteria by introducing the genes which code these substances. In this way bacteria can be used as bio–factories for synthesis of these substances.

(c) Insulin is medicine used for the treatment of diabetes. Initially it is derived from animals (pig and cows) but today it is produced by gene splicing.

(d) Hepatitis B is a viral disease of liver. Today a vaccine is prepared with the help of genetic engineering.

(vi) **Application of genetic engineering in industrial uses (Biotechnology)**

Biotechnology is a branch of genetic engineering. Biotechnology includes all industrial processes mediated by the activity of micro–organisms. Other important aspects of biotechnology beside its application plant, tissue culture, genetic engineering, embryo transplantation, biofertilizers, test tube babies etc. are In production of various food products and beverages, Enzymes, Hormones, Vitamins, Pharmaceuticals, Antibiotics, Antibodies, Vaccines, DNA probes, Amino acids, Organic acids, Proteins, Interferons, Biosolvents and Biodetergents.

(a) **Human insulin :** In 1982 genetically engineered **Human Insulin** or **Humulin** was produced which was sold in the market. It is produced by *E. coli* that contains genes that are chemically synthesized. This bacterially produced insulin can be obtained in unlimited quantities which is as effective as animal insulin for use in the treatment of diabetes. Insulin is made up of two polypeptide chains 'A' and 'B', of which chain 'A' is made of 21 amino acids and B is made of 30 amino acids linked by disulphide bonds. The sequence of amino acids in these chain was worked by **Sanger**. It can also be produced by using modified baker's yeast. This secretes proinsulin precursors into the fermentation medium, which is easily purified and converted into biologically active human insulin in a single enzymic step. The main steps involved in the biotechnologically synthesized human insulin are as follows.

(1) For the synthesis of insulin RNA is extracted from β cells of Islets of Langerhans of pancreas of animal.

(2) By the enzyme reverse transcriptase single strand of DNA complimentary to mRNA is synthesized.

(3) Second strand of DNA complimentary to first strand is synthesized by enzyme **DNA polymerase**.

(4) The above two strands of copy DNA is joined to plasmid by using an enzyme called terminal transferase.

(5) The two ends of DNA are annealed by an enzyme called **ligase**. Thus the ends of inserted DNA and plasmids DNAare sealed and a new circular plasmid is formed. This is a molecule of **recombinant DNA**.

(6) This recombinant DNA molecule is inoculated in a new bacterial cell of *E. coli* and inserted in a bacterial gene after having cut by a restriction enzyme.

(b) **Growth hormones :** Human growth hormone or somatotropin is secreted by anterior lobe of pituitary and its deficiency results in dwarfism. It is species specific and consist of 191 amino acids. Biosynthesis of somatotropin was carried out by Goeddel and his coworkers at Genetech For this cDNA for human growth hormone was inserted in *E.coli* chromosome, close to that gene which codes for enzyme β–**galactosidase** by pBR_{322} plasmid. A micro–organism *Pseudomonas aeruginosa* secretes and correctly processes human growth hormone.

(1) Clone is a repopulation of cells or individuals which are genetically identical.

(2) There are two types of cloning, gene cloning at molecular level and cloning of organisms.

(3) Cloning is meant for preservation of the genotype of the organism.

(4) Ian Wimut of Roslin Institute, Edinburgh, U.K. has produced a clone of adult lamb named Dolly.