

Is Inbreeding Harmful?

Inbreeding is mating within a mendelian population. It refers to mating individuals of similar/same genotype.

Effects: Increases homozygosity & reduces heterozygosity thereby reducing genotypic variability.

Ex: Caste System [It is M. P.]

Supporters give example of Great Andamans.

$73000 \rightarrow \sim 28$  (1971 census) they attribute it to inbreeding.  
(300yrs)

① They argue that 'if' there is present an autosomal recessive lethal / sub-lethal gene; & since inbreeding increases the homozygosity the moment the recessive allele becomes homozygous its phenotype appears. Thus NS immediately operates on it & eliminates that particular individual. Thus they say inbreeding is harmful.

But they also say 'if'; so they also agree that inbreeding itself is not harmful but it is the presence of the autosomal recessive lethal / sub-lethal that is the worry.

Ex: Pure breeding / Inbreed of crop varieties

Ex: Darwin & Cleopatra

Ex: South Indians : also South Asian countries have caste system yet pop^n boom. Mendelian Pop^n

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The recessive lethals have already been lost in the past; & the resulting genotypes are causing the population boom.

- ② If we follow Mendel's Monohybrid cross then  $F_2: \frac{1}{4}$ th  $\rightarrow$  Homozygous for recessive trait. Thus they would be eliminated. So critics argue that in every gen.  $\frac{1}{4}$ th of the population would be lost, due to inbreeding.

But Malthus says that human's have enormous fertility which can compensate for this loss. So actually popn will never decrease.

- ③ Some argue that genotypic variability reduction is dangerous as if there is change in env & # of genotypes is less then that species may not survive that change. If # of genotypes was more than some of the genotypes may have had survived & as a consequence the species might have survived.  
 ↳ Neither study or evidence for Man.

- ④ Only in 1 condition inbreeding can be harmful; when the survivors cannot compensate for the loss due to less fertility. Then inbreeding may be harmful in small isolates.

But in general humans have sufficient fertility, so whether inbreeding is harmful is a mere theoretical

Not of  
realistic  
concern

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issue. Thus issue of harmful effects of inbreeding is not an issue of human genetics but that of population genetics i.e. whether popn survives/ and survives better or not.

Therefore without holistic understanding of env & eco & ♂ & ♀ preferences; simple blanket statements saying "inbreeding is harmful" is wrong.

Case Study: Rao & Imbaran (1977)

Brahmins of TN don't show inbreeding depression as bad alleles are long eliminated.

Case Study: Shah & Sinha (1984)

Ansari Muslims of Bhagalpur in Bihar show inbreeding depression; as bad alleles are present. They were initially tuharu's who didn't practice inbreeding & converted only 400yaq & adopted this practice.

⇒ Can utilise in Inbreeding ♀ also.

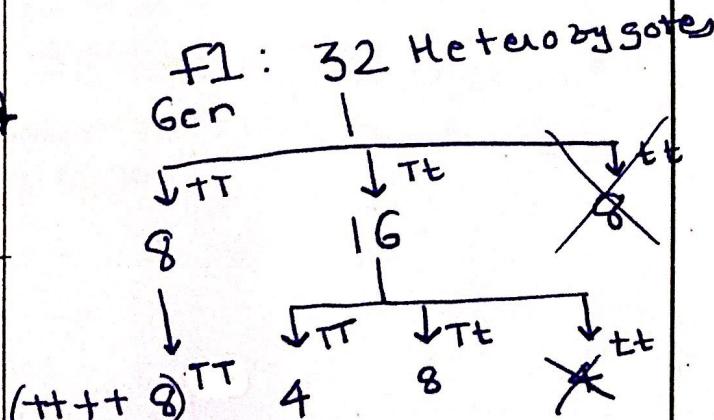
Great Andamense popn has again increased. (How?)

In past, their Cultural practices & WW2 had affected their population.

Sohay VS 2020 ⇒ 54;

R.B called them as "Andaman Islanders" where

he found 10 communities but only 3 are left now → 54



- Homozygosity (↑)
- Bad alleles eliminated
- But remaining can easily compensate for their loss

## Genetic Effects of Consanguineous & Non-C matings + C.M.

Consanguinity refers to mating between individuals related by blood who have a common ancestor a few generations ago. However degree of consanguinity varies. Ex: M-S / F-D / B-S very taboo in most <sup>SCGs</sup> & called Homoamy (Highly consanguineous)

But many societies promote C.M. & Endogamy. Ex: Amish in Pennsylvania, etc.

↳ Elaborate C.M. with appropriate examples.

Thus we compare: <sup>①</sup> Consanguineous → Inbreeding  
<sup>②</sup> Non-consanguineous → Hybridization

### Case Studies

- ① Rao & Imbaran (1977) : Brahmins of TN
- ② Shah & Sinha (1984) : Ansari Muslims of Bhagalpur, Bihar
- ③ Japanese : 10% CM (1<sup>st</sup>)  
Andhra : 10% U-N
- ④ Population of Koda, Paliyan, etc of Kerala decreasing due to consanguineous marriages. (2014)
- ⑤ Afzal (1984) : Consanguinity reduces 14% of the progeny.

## Non-consanguineous Mating :

- a) Positive Assortment : Similar phenotypes mate with each other. It ( $\uparrow$ ) homozygosity.
- b) Negative Assortment : Opposite; many times found heterozygosity confers survival value.

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Indel  
Polymer  
Phism

Single  
Nucleotide  
Polymorphism  
(SNP)

In  
De Novo  
means not  
inherited  
from parents.

## Aberations

### [Diagrams]

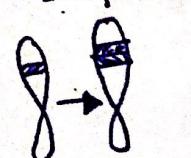
#### Chromosomal

##### Structural/Morphological

##### Intra-chromosomal

→ Deletion

→ Duplication · Chancot Manie  
· Tooth Disease  
Type 3A.



→ Inversion

→ Ring formation, — — —  
→ Isochromosomes (PTO)

Inter-  
Chromosomal

→ Translocation (exchange)

→ Addition

(only 1 sided)

#### Numerical

##### Euploidy

→ Increase in  
set's of the  
chromosomes

$2n; \rightarrow (3n, 4n)$

##### Anueploidy

Hypo  
( $< 46$ )

Hyper  
( $> 46$ )

→ Monosomy → Trisomy

→ Nullisomy → Tetrasomy

##### Autosomal

##### Sex-Linked

Anueploidy Can be partial also  
which is different from the  
Mosaicism.

FULL Anueploidy → Meiosis Non-disjunction

Partial Anueploidy → Meiosis Translocation

Mosaicism → Non-disjunction in Meiosis. De Novo means not inherited from parents.

#### Genetic

##### 1. Inversion

##### 2. Substitution

→ The length remains same

a) Transition: same Δ group

$A = \text{[T]}$   
 $G \equiv [C]$  → Pyrimidines

b) Transversion: diff Δ group

c) Tautomerism: Aldehyde to ketone  
It is reversible. (H-bond)

##### 3. Frame Shift

a) Insertion: Add base

b) Deletion: Subtract base  
Here gene length changes.

##### 4. Point Mutation

→ Change in 1 base pair & is type of  
Substitution only.

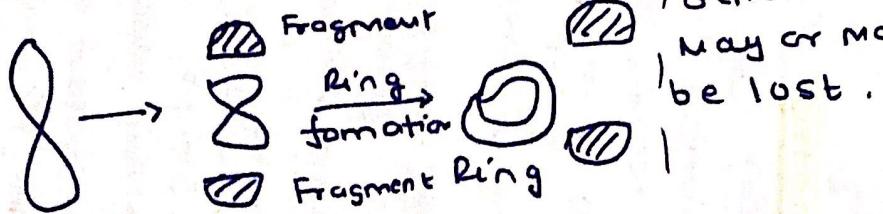
## Chromosomal Abberations Data

60% Mom	1. Harry (XXY) Klinefelter	1940	1/850 M-B
70% Dad	2. Henry (XO) Turner	1938	1/3000 F-B
Majorly Mom	3. Patricia (XXX) Jacobs	1959	1/1000 F-B
Non-Inheritable	4. Petria (XYY) Jacobson	1973	1/1000 M-B
— — —			
3% Trans- location	1. Langdon Down (21+)	1866	1/700 (LB)
90% < 14y Sub-Lethal	2. John Hilton Edwards (8+)	1960	1/8000 (LB)
93% < 14y Sub-Lethal Avg = 19 days	3. Klaus (13+) Patton	1960	$\frac{1}{(10 - 21.7)} K (LB)$
— — —	4. Lejeune [5P]	1963	1/50 K (LB)

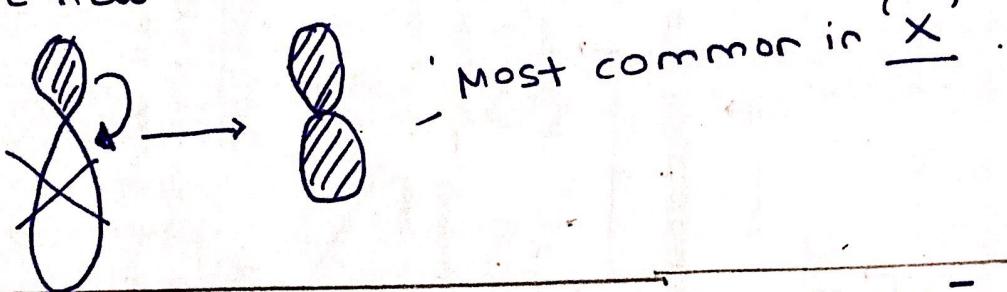
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## Additional Information

Ring:



Isochromosome: Deletion of one formed & then duplication of remaining one which attaches itself in an inverted way. thus the new structure is symmetrical.



Ex: Jacobson Syndrome  $\rightarrow$  Terminal 11q<sup>-</sup>

Wolf Hirschhorn "  $\rightarrow$  Partial 4p<sup>-</sup>

Chronic Granulocytic Leukemia  $\rightarrow$  22q<sup>-</sup>

Barr Body = (No of 'X' chromosome - 1)

$\therefore$  Turner  $\rightarrow$  0 ; Klinefelter  $\geq 1 \frac{1}{2}$   
women men

$\rightarrow$  OY not a viable zygote.

$\rightarrow$  Monosomy deadlier than Trisomy as loss of information. Monosomy of autosomes more lethal.

$\rightarrow$  Polyploidy of Autosomes deadlier as they are longer.

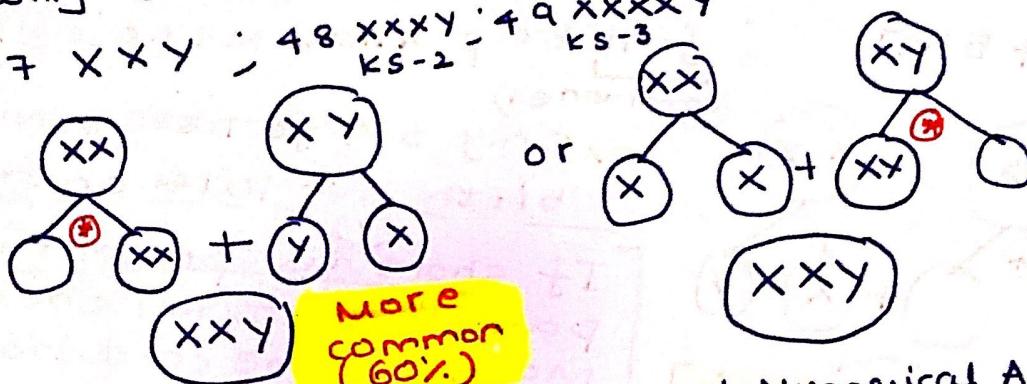
$\rightarrow$  Women usually more affected by the non-disjunction & occurs in Anaphase of Meiosis I mostly.

1

Klinefelter Syndrome (Male Hypogonadism)

Harry Klinefelter ; 1940 :  $\frac{1}{850}$  male births

$47 \text{ } XXY$ ;  $48 \text{ } XXXY$ ;  $49 \text{ } XXXY$   
KS-2 KS-3



It is a sexual Chromosomal Numerical Aberration.  
Characteristics

→ Small testis which are sterile [NO SPERM]

→ Gynaecomastia (protruding breasts)

→ Lack/less secondary male characters such as beard, chest hair, etc. Only outwardly male.

→ Tall → Long Legs & fat near hips like female.

→ Female type pubic hair.

→ Normal life expectancy & intelligence.

→ Narrow shoulder & wide pelvis.

→ Less baldness; low testosterone.

way-forward It affects

→ Avoid old age pregnancy as ova & spindle fibres weak

Common to all

→ Karyotyping at Birth & Genetic Counselling.

→ Assistive Reproductive Technology

→ Breast Removal.

→ Testosterone Replacement

→ Speech therapy

→ Social attitudinal change.

→ Males with small testes to be checked.

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## ② Turner's Syndrome (Female hypogonadism)

Henry Turner ; 1938 ;  $\frac{1}{3000}$  female births

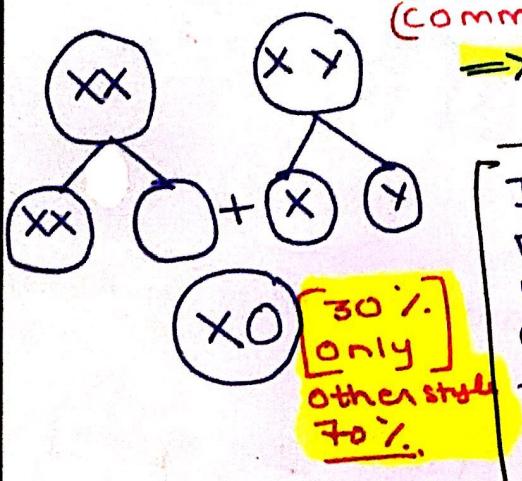
$45\text{XO}$  ; full or partial monosomy

(common)

$\Rightarrow$  Only 3% foetuses survive  
birth but later on fine.

If short arm present in  
partial monosomy then  
many of the conditions  
can be avoided.

If only long arm (q) is  
present  $\Rightarrow$  Short stature.



### Characteristics

- Main cause of female infertility.
- No menstruation; No ovaries.
- Poor breast dev; short stature,
- Normal intelligence & life expectancy.
- Webbed Neck; Nevi (brown spots).
- (cystic hygroma)
- Constriction of Aorta; Heart, kidney /
- Diabetes, malformation possible,
- Low posterior hairline
- Broad chest with wide spaced nipples.

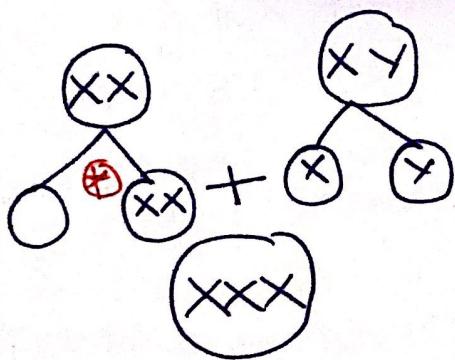
### Way - forward

- Therapy with oestrogens that help with secondary sexual characteristics.

(3)

Superfemale Syndrome

Patricia Jacobs, 1959,  $\frac{1}{1000}$  female births  
47XXX

Characteristics

- No distinctive phenotype; tough to diagnose.
- Occasional mild dev issues like learning disability or speech delay in child.
- Anxiety, Poor self Esteem, Depression & Poor coordination; Poor muscles.
- Produce normal children
- Tall; Small Head; 5th finger curves to 4<sup>th</sup>.
- More width between eyes.
- Can live normal lives.

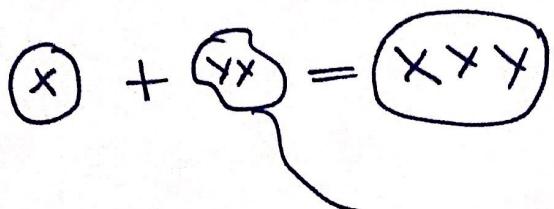
way-forward:

- 90% of affected not diagnosed due to very mild symptoms.

(4)

Jacobs Syndrome [Criminal Syndrome]Petrea Jacobson; 1973 ;  $\frac{1}{1000}$  male birth

47 XYY ; Remote stigma Attached.

Characteristics:

- Normal fertility
- No obvious changes
- Not inheritable

Others → Fragile X syndrome  
 Others → Chimera

**U.P.S.C.****① Down Syndrome (Mongoloidism)**

Langdon Down; 1866;  $\frac{1}{700}$  is frequency.  
(British Physician)

$47 \text{ } XX + 21$

$47 \text{ } XY + 21$

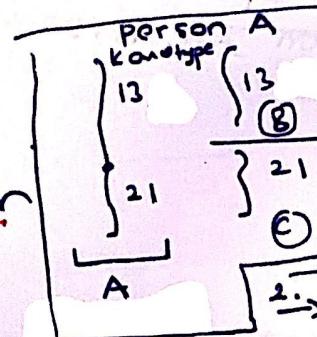
① Non-disjunction  
during Meiosis.

Types  
② Robertsonian  
Translocation

13 Trisomy  $\rightarrow$  Patau

1959 Lejeune showed  
that partial 21 trisomy  
also possible.

$\Rightarrow$  Full 21 Trisomy



If gets A + B/C  
then he/she becomes affected  
 $\Rightarrow$  translocation carrier if only A  
but otherwise

Characteristics: 21 Trisomy,  
1. no effect  
If B & C then perfect.

→ Most common & best known chromosomal numerical autosomal abberation.

→ Autosomal Semi-Lethal.

→ 75% foetuses Miscarry.

\* → Doesn't vary due to paternal age; but maternal age affects especially  $> 40$ . Then children have  $(\frac{1}{50})$  chance.

→ Life expectancy ~60y due to not incarcinating people & better assistive.

→ Severe Mental Retardation [IQ at 50  $\Rightarrow$  ~9y old]

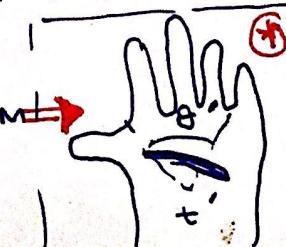
→ Growth failure & Epicanthic fold with slanting eyes.

→ Excess skin at back of Neck.

→ Congenital heart disease

→ Simian crease found in Palm  $\rightarrow$

→ Wrinkled Tongue & large.



- fingers have loops in print region rather than arches/curls. → 
- Loose Joints & Stubby Hands

### Way - forward

- Remove racial overtones, & idiocy connotations.
- India posses max cases
- No known cure ; but stem cell injection in affected babies body can cure it?
- Can be found during pregnancy [Amniotic fluid]
- Physical therapy for motor-skills.
- Speech Therapy also helps.

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(2)

Edward Syndrome : 18 Trisomy

John Hilton Edwards ; 1960 ;  $\frac{1}{8000}$  humans

$47\text{XX}(+18)/47\text{XY}(+18)$

→ Standard Diagram

& Partial possible too

→ Even Translocation

Characteristics

- Small triangular mouth (micrognathia) & flexed fingers.
- virtually every organ system develops abnormalities. E.g.: Breathing, heart, kidney, etc.
- 90% die within their 1st year [sub-lethal].
- Rocker bottom feet & low weight
- Small & abnormally shaped head [microcephaly]
- Intellectual disability. (prominent occiput)

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3) Patau Syndrome : 13 Trisomy

Klaus Patau; 1960;  $\frac{1}{10K} - \frac{1}{21.7K}$  humans

$47\text{ XX} + 13 / 47\text{ XY} + 13$ ;

[Standard Diagram]

→ Partial Possile ✓

→ Translocation ✓

Characteristics

→ 93% of children die < 1 yr, sub-Lethal

- Median Life expectancy → ~1+ days.
- \* → Cleft Palate [Opening in roof of mouth]
- \* → Small abnormally shaped head (microcephaly).
- Severe Mental retardation & gross brain malformation.
- Polydactyl (extra digits) overlapping w/ clenched position.
- Close set eyes; slit in Iris;

④

Cri-du-Chat: 5p<sup>-</sup> Syndrome

Lejeune; 1963 ; Frequency =  $\frac{1}{50k}$  live births.  
called '5p Monosomy'.

$46XX5p^- / 46XY5p^-$

P  
short arm  
 $\frac{1}{2}$  -  $\frac{1}{2}$   
Partial  
Break

5p<sup>-</sup>

In 1 of  
the 2  
chromosome  
only

→ 90% of cases from  
sporadic/randomly  
occurring 'de novo' deletion  
& rest are due to  
translocation.

### Characteristics

{ → Autosomal Structural Chromosomal Abnormalities  
→ Maternal age has no impact.

\* → If survive 1st year; many lived to age  
of 50. Hence it is Semi-Lethal.

- \* → Cat like cry from affected children.
- \* → Widely spaced eyes with epicanthic folds.
- \* → Small abnormally shaped head [microcephaly]
- \* → Intellectual disability & behavioural problems.
- Edema in hand / feet; Excess nuchal skin.
- Congenital heart disease;
- \* → Moon like face;

Few  
like,  
XXX

### way-forward

- Physical & Speech Therapy.

⇒ Always start 22 P + 1 P : Terminology  
→ Diagram → Characters  
→ Remedies if any

## Cultural Effect

→ Age of Marriage has direct affect  
on Chromosomal Aberration.



## Genetic Counselling

Expert Counselling by a geneticist regarding genetic problems is called as G.C.. It is most imp appn of mendelism. } Harper

Who visit them? 2 types usually:

- Couples who have long history of disease in the family & who want to go for a child.
- Those from different families (with history of some diseases) who seek advice regarding marriage.

The person who is infected is called as probund/Prostista which forms base of the analysis. Also many people are shy to consult a geneticist due to various reasons. The person seeking such advice is called as "consultant". There are 5 stages to it:

- ① History & Pedigree Reconstruction He has catalogue  
of over 5000 conditions.
  - Need standard medical history of Proband & of any other affected members in the family. The inheritance pattern of the disease if already not known is ascertained. \*
  - good use of space
- ② Examination & Confirmation
  - More medical tests may be needed.  
Ex: DNA Probe, Glucose Test, etc. Any particular family member or the proband may need these further tests.

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③ Diagnosis: The Pedigree & Medical Investigation may lead to a confident diagnosis or further diagnosis may be required. Only after a detailed & confirmed diagnosis the further steps are taken.

④ Counselling Interview: It should be non-judgemental & non-directive. Adequate time for questions & tune advice to educational background of consultant. Both parents must be counselled. Cosy office & 100% anonymity. Tell family about socio-economic & psychological disabilities too. Clears doubts & misconceptions. Tell probabilities & mode of inheritance. Ex: 1/4 chance doesn't mean next 3 children are normal. Give them treatment possibilities & when the exact diagnosis would be possible. Pre-natal tests must be told of.

<u>Ex:</u>	{ Cleft Lip/Palate, Adbinism → Birth Eosinophilia → Early childhood Duchenne Muscular Dystrophy → Adolescence Huntington → 60 - 70 years Alzheimers } { Give already known example }
<u>Time of occurrence</u>	
<u>Mode</u>	
<u>Treatment</u>	{ Cleft Lip → Plastic surgery ✓ ADA deficiency } Bone marrow SCA Tep. [Gene Augmentation] B-cell Leukemia → Yes can Gene Therapy

Advice: If autosomal recessive Lethal/sub-lethal then advisable not to marry close relatives.

- ⑤ Follow - UP : If needed or when new opportunities arise. As & when Gene Therapy develops its scope & application will be much more.

### Challenges

- Science not conclusive; probabilistic & not deterministic.
- Inheritance may be complex → Scope of error.
- It might also show variable expression.
- Wrong data given: Abortions, Consanguineous matings & miscarriages hidden.
- Non-penetrance & Gonadal Mosaicism.
- Need further dev in Genetic Engineering.

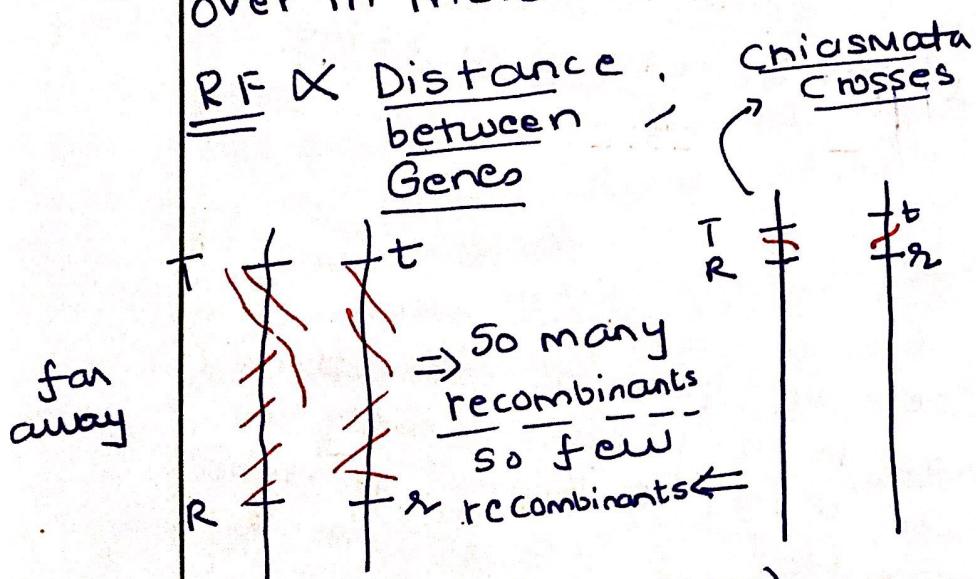
In all cases of genetic counselling; the geneticist has to act not merely as a counsellor but as a social Reformer. He clears the lifetime anxieties of the couple & brings joy & Certainty to their lives.

- American Soc'y of Human Genetics regulates it USA.
- Sometimes G.C. ⇒ Also recommend to adopt children.

## Gene-Mapping

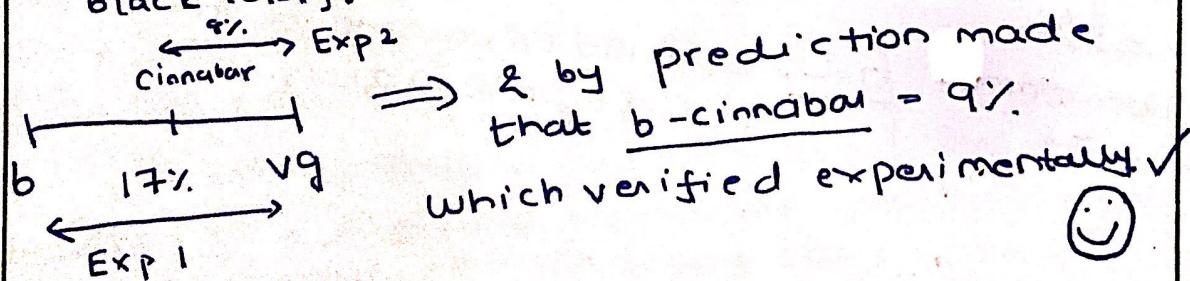
Methods used to identify locus of gene & distance between Genes. The Gene Maps so created help describe the spatial arrangement of genes on a Chromosome.

① Linkage Maps: It shows the relative position of genes wrt each other in terms of recombination frequency. The RF is a measure of probability of the segregation of 2 genes during crossing over in meiosis. Therefore: aka Crossing over Maps.



Ex: Drosophila (Fruit flies)

Sandy color, normal wing, normal eye color: Normal  
black color, vestigial wing, cinnabon eye color: Mutant



Note: Max RF = 50%. i.e. the genes lie on different chromosomes hence the allelic crossing is completely random. It never exceeds 50%.

Thus Gene Mapping helps us in understanding & finding out genetic markers also.

② Physical/Molecular Maps: Physical distance

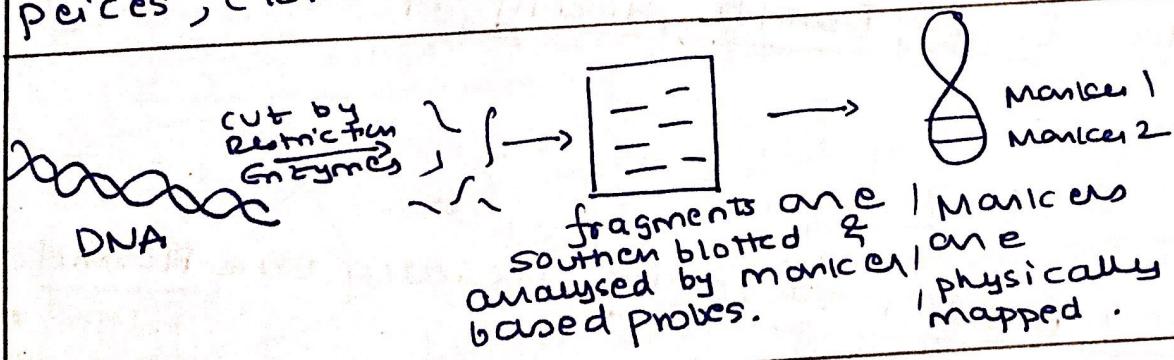
between different genes in terms of number of base pairs [ATCG] between them. Thus we can find the exact location on the chromosome. It is of 2 types:

a) Restriction Mapping

b) Contiguous Mapping:

Here DNA is broken down into very small pieces, cloned & base sequence analysed.

Used by HGP to map 99.99% of <sup>both used</sup> human genome.



③ Cytological Maps: Somatic cell Hyb<sup>n</sup>; In-situ Hyb<sup>m</sup> & Linkage studies are used to make it

Advantages:

- Evolutionary studies of humans & ancestors.
- Knowing Maps of plant & animals  $\Rightarrow$  Agri Apps.
- Helps Gen. Counselling, forensic (A), Gene Therapy
- Diagnosis of diseases - finding targets of new age drugs.
- Concern about 'designer babies' & sex-selection.
- Only getting better with time.

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## Recombinant DNA Technology [20M]

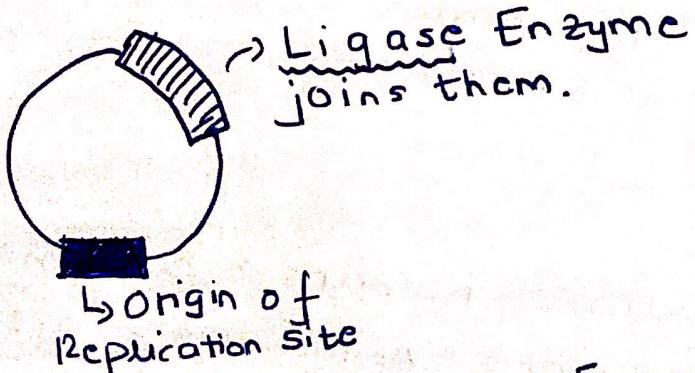
Dev in 1970's by Herbert Boyer, Stanley Norman Cohen & Robert Swanson. 1st - Biotech company was Genentech in 1976.

- ① Generation of fragments: Using restriction enzymes to cut at appropriate places.

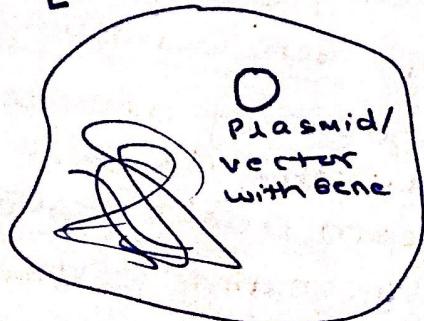
Ex: EcoRI, BamHI, HindIII, etc.

- ② Incorporate into Vector: Usually the Plasmid of a bacteria.

Lconfers  
Anti-Biotic  
resistance.



### [TRANSFORMATION]



- ③ Introduction into Host:

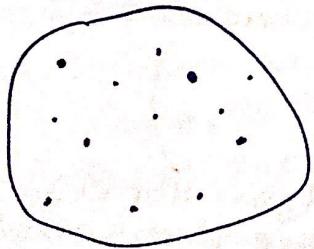
Ex: E coli; it produces more copies of the Gene for us.

→ Agitate Ecoli to take up plasmids.

④ Screening of the Ecoli Colonies: To get the bacteria which has our target gene.

To ensure only E-coli with plasmid grow USC Anti-biotic & all the E-coli without the plasmid die. Note that plasmid has ORI, Target Gene & "Antibiotic Resistance" gene also.

↳ Then a library is generated of the E-coli colonies with plasmids.



⇒ To get final gene we do: "cloning by function" / "cloning by complementation".

↳ Then there is c-DNA → RNA from rRNA by R.T. enzyme.

⇒ Ultimately we can get E-coli to make us our target gene by complex techniques.

Applications: → Biofuel & Bioremediation  
→ Enzymes: Renin in cheese.  
→ GMO's ✓

→ Synthetic Vaccines are produced. (BG also)  
Ex: Rabies, Cholera, Typhoid, Polio, etc.

→ Hormones & Protein Synthesis

Ex: Insulin, GH → Somatotrophin ; Urokinase → Dissolve clot during heart attack  
GH → Somatostatin ; Factor IX & VIII → To clot i.e. blood (Haemophilia)

National Dairy Research Institute biosynthesised insulin from buffalo milk through L-DNA tech.

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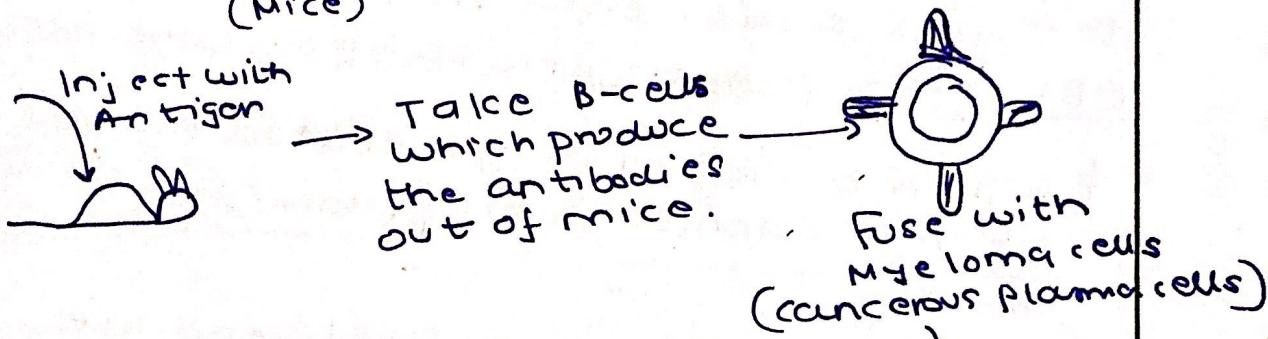
→ Use in Gene Therapy especially Augmentation.

Ex: ADA deficiency, Yescomta Gene Therapy.

→ Creation of DNA probes which help in diagnosis of many diseases like Malaria, kalaazar [Leismania], Elephantiasis (with Wuchereria) etc. Short fragments of DNA to identify complementary sequences of DNA.

→ Monoclonal Antibodies:

Based on Mutine Hybridoma technology.  
(Mice)



Lot of same antibodies are produced like B cells but are produced & replicate like in culture hence tumor cells "Monoclonal".  
Hybridomas are produced

→ Can even be used as diagnostic tool to detect pregnancies.

→ Gene Mapping & understanding structure & function of gene. ⇒ Agarose Gel Electrophoresis & shotgun sequencing.

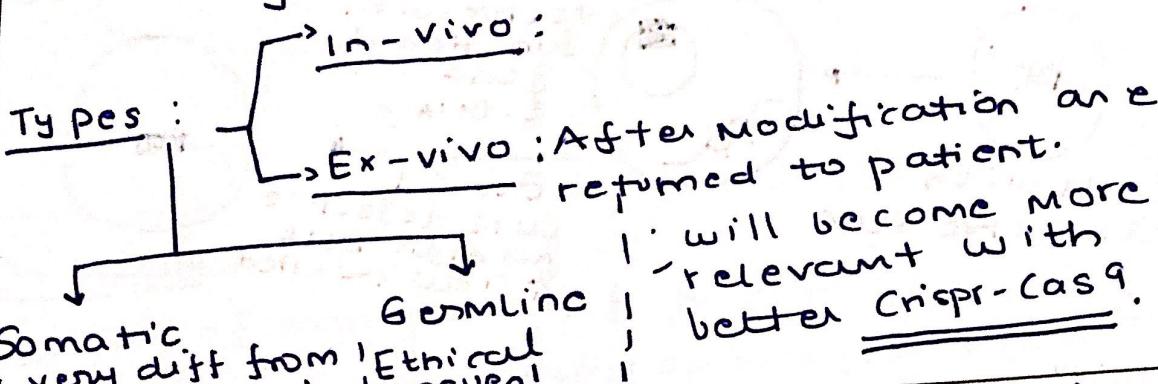
→ Agriculture: N<sub>2</sub> fixation; HYV.

→ Physical & Biological leaks & contamination & biohazard risk.

→ Ethical issues: Patentable, cloning, 2 species? Stem cells, Aim, Means, etc.

Gene Therapy : French Anderson in 1990: 4 year old girl with ADA.

Insertion of Genes into an individual's cells as a drug to treat diseases.



① Gene Augmentation : Most successful & only working method. Used if we have a non-functional gene. Then we can add the working copies of the gene. The gene may be inserted in a new location also & it treats the monogenic disorders. The genes are introduced by vectors such as Retroviruses & Adenoviruses.

Ex: Adenosine Deaminase(ADA) deficiency leads to immuno deficiency. Most successful here. (SCID)

Ex: Sickle Cell Anemia; Cystic Fibrosis, Thalassemia, etc. + [Duchenne Muscular Dystrophy]

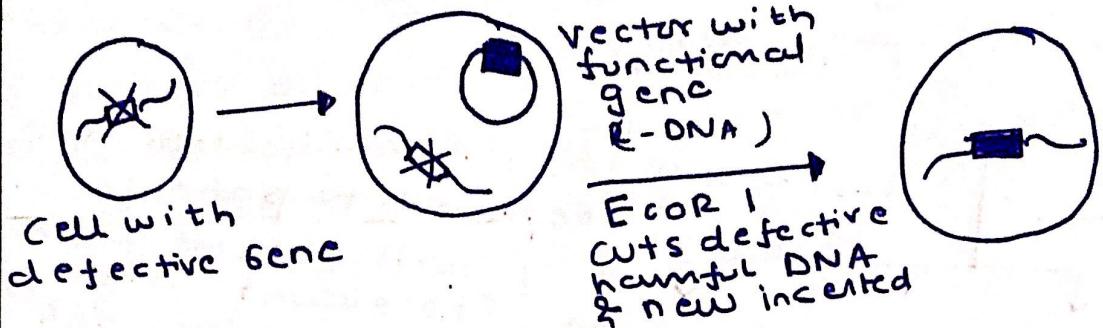
⇒ Gene Gun [Hclium]; Micro-manipulation, Ca Phosphate & Electric currents also used to insert the DNA.

The inserted gene is called Episome.

Ex: Yescata CAR-T (WBC) cell therapy for B-cell Lymphoma treatment.

② Gene-Replacement: A defective harmful gene is removed. Not achieved yet & realistic in embryo / germ cells.

cell functioning property



③ Gene-Targeting: Knock in/out mechanism.

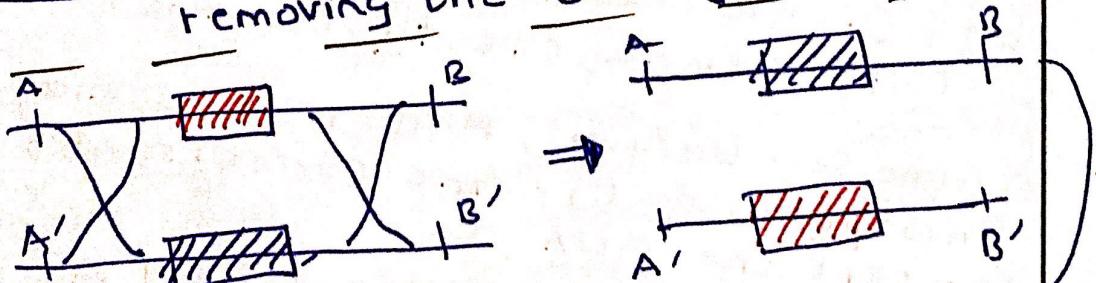
Correction of defective harmful gene by introduction of complementary part via homologous recombination.

\* Knockout: Make bad gene silent. [This is major one here]

→ Knockin: Add a functional gene by removing the bad gene.

Target Gene  
Ex:

Selectable marker  
homologous



Mostly done to '1 gene of 2', Not yet feasible way.

Criticism:

- Control of expression of foreign gene: time & rate.
- Avoiding immune response triggered by the intervention, enzymes of body shouldn't degrade gene.
- Germ cell → Ethical concerns. Gene should integrate fast into host especially tough to diff in embryonic stage.
- Avoiding enzymatic degradation & disruption in functioning of neighbouring genes.
- Single Gene ✓; but can't cure chromosomal aberrations or polygenic defects.
- Getting the gene into enough # of cells & the right cells.

Ex: Hyderabad Child → Spinal Muscular Atrophy  
given Zolgensma injection worth 16cr through crowdfunding.

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## Genome Study [10M]

Genome refers to complete genetic information (range of genes) carried by an individual or found in a given species.

Gene pool on the other hand refers to all the possible allelic variations of every gene in the population.

→ Francis S Collins, Eric Lander & Anthony Fauci.

HGP: Goal was to sequence the human genome. The idea dev in 1986 by Renato Dulbecco to find out the cancer causing genes. It started in 1990 under aegis of NIH, USA.

① Pure Gene → cut by ② restriction enzymes → fragments → ③ Analyse them computer program

It is called as Shotgun-Sequencing. It is one of the fastest methods known.

HGP 1st Report, 2003:

- far fewer genes than expected, rest of genome is junk. ⇒ 26K; only 1.1% of total.
- 99.99% of human code similar; so Myth of Racism busted. Many times across races are more similar than within races.
- Also RoOA: Max genetic diversity in Africa & Link with founders effect. It also meant greece is not source of the western civilization.
- 223 genes one from bacteria.
- All current drugs target only 483 diff biological targets in the human body.

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The project has revealed many new target sets for gene therapy, & also genetic counselling.

After completion of Human Genome Project, many other projects have been started. One such project is Human Genome Evolution Project. This project aims at comparing the genome of different species to understand the evolution of life forms. Another project is Human Epigenome Project. This project aims at understanding the changes in gene expression without changing the DNA sequence. These projects have provided valuable information for medical research and genetic engineering.

Similar project taken up for H.n : Neanderthal Genome Project (2006).

Recently HGP-White Project started in 2016. To chemically manipulate DNA & ultimately synthetically create an entire human genome.

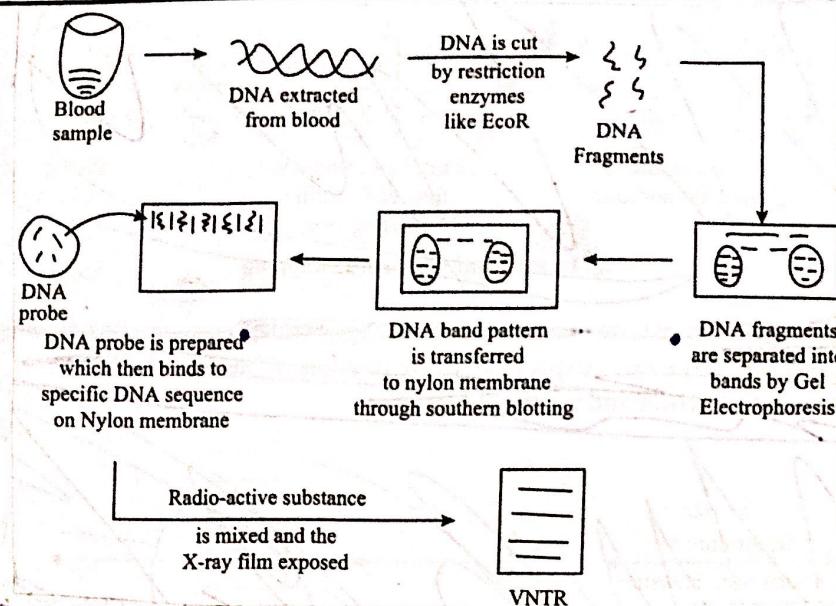
**DNA Profiling**

~~Species is identified by DNA~~  
~~of house hold~~  
~~of DNA~~  
~~HU~~

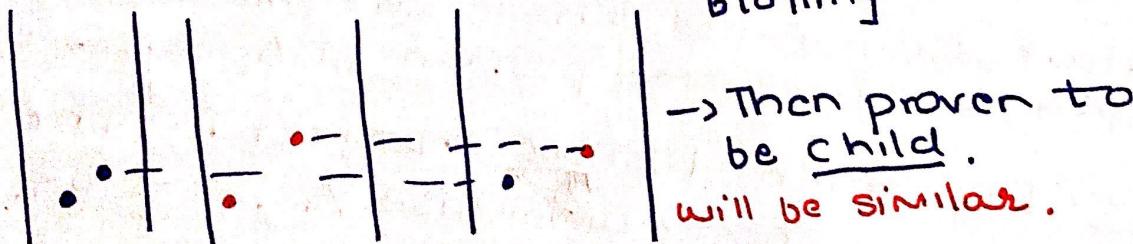
It is a technique by which individuals can be identified & compared through their respective DNA characteristics. It is thus also called as DNA fingerprinting. The founder was Sir Alec Jeffreys in 1984.

99.99% of human DNA sequence is the same in all humans. But particular sequences of repeating patterns in DNA called as Variable Number Tandem repeats (VNTR) are unique to each human. Thus VNTR forms the basis of DNA fingerprinting.

Applications :- Paternity & maternity disputes.  
 → In forensic A for criminal invs & personal identification.  
 → Medical info like allergies & susceptibility to diseases.  
 → Genealogy studies



$(P_1) + (P_2) = \text{Child}$ ; Gel Electrophoresis blotting



→ Naina Sahni case solved by this method.  
(Tandoor Kand)

Recently DNA technology (Use & Regulation) Bill,  
2017 introduced. It shows the contemporary  
relevance of this field.

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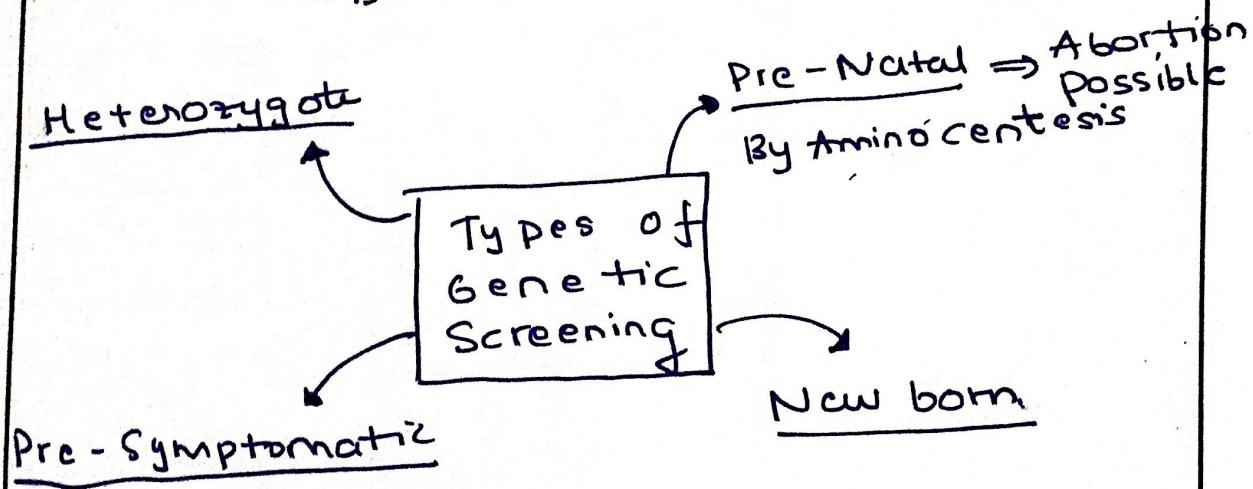
## Genetic Screening

Refers to the application of tests to groups or individuals for the purpose of detecting carriers of deleterious genes or chromosomal rearrangements.

Additional epidemiological data can also be collected. It also be very useful in Genetic Counselling. The choice of which group to screen depends on the type of the disease.

expand knowledge of diseases

Some can be detected at birth itself.  
Ex: PKU, Galactosaemia [Inborn error of metabolism]  
of sugar Galactose  
↳ Blood test of newborns.



→ Hair, Skin, Blood, Tissue are examined for specific chromosome, protein, DNA, markers, etc.

Ex: Tay-Sach's Disease → defect in the enzyme hexoseaminidase A. 3-5 yr

life expectancy & common in Jews of Central/eastern Europe. It can be detected at foetal stage itself.

Homozygotes → Aminocentesis.

Heterozygotes → Simple blood test.

Ex: Haemophilia, Duchenne Muscular Dystrophy, etc.

- GS can be predictive as well as diagnostic
- Methods: karyotype, ultrasound, Aminoacetonates, Blood sugar, expression, etc.

Genetic Panels are dev when scientists identify mutant genes that cause diseases in specific populations. Currently, India relies on European Panels except for pre-natal diagnostics which are not oriented towards Indian pop<sup>n</sup> as mutant genes differ across different geographical regions.

### Challenges

- Institutionalising of children who are diagnosed.
- In India; very expensive & painstaking due to dependence on European Genetic Panels. We need to develop indigenous ones.
- Might make little difference to the prognosis of the individuals.
- Often abortion recommended → Not suitable in many societies.
- Issues of scale.
- Ethical Principles: reveals his risk profile & also that of offsprings.
- Data concerns → Life & Medical Insurance companies.
- Only probabilistic & not deterministic.
- Many cannot be diagnosed in-utero.

## Genetic Imprinting

Differential inheritance of genetic material from mother & father.

Mendel had given "Theory of Equivalence" which says there is no difference in expression of same gene inherited from male or female.

But it is visualised that male & female contribution to genome is not fully equivalent & f^n of chromosome may differ depending upon whether it is paternally or maternally derived. The paternally derived genes control early dev of placental tissues whereas maternally derived genes play imp role in dev of embryo proper.

Thus in humans some genes are inherited markedly different from male & female parents.

### Mechanism:

Selective Methylation of Genome in the Gametes. The Enzyme methylase adds  $-CH_3(\text{Methyl})$  group to carbon 5 position of the Cytosine & Guanine bases. Usually ova are more methylated than sperm.

Ex: In females, one of 'X' chromosome is inactivated. The methylation of the inactive chromosome is given to Imprinting although It affects the entire chromosome & not dependent upon gender of parental origin.

thus it implies that in certain cases a genetic defect will only produce a

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phenotype if inherited from a particular parent.

Ex: Chromosomal deletion in region controlling placental dev may have no effect if inherited maternally but may cause failure of placental dev if inherited paternally.

Prader-Willi Syndrome | Angelman Syndrome

Paternally derived deletion of chromosome 15q, 11-13. Maternally derived deletion of chromosome 15, 11-13.

- developmental delay
- happy disposition
- obesity
- mental retardation
- hypogonadism
- hypotonia in infancy
- toxic movement
- obesity/uncontrollable appetite
- large mouth protruding, tongue.
- seizures.

Ex: Huntington's Chorea : Autosomal Dominant Source can be male or female (paternal or maternal). The symptoms are same but severity & time of expression are a bit different. ⇒ lower if PE6.

Characteristics: Ex: Fragile X Syndrome

- Imprinted Genomes express variably: time ↑ & magnitude
- Imprinted Genomes
  - Species specific; Not a rule; Implicated in many diseases. → Doesn't change DNA sequence.
  - They remain fixed in mitosis; but are erasable in meiosis as the chromosomal must be newly imprinted depending on the gender of its host.
  - Son inherits highly methylated genes from mother & erases these methylation in his gonad before passing on to offspring.
  - Genes are switched on/off by imprinting.

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Ex: Growth genes turned off once growth over.  
This switching can be temporary / permanent.

We receive 2 alleles of every gene.

**Impact**  
each  
other

MES → Maternally exp gene { Genomic imprinting }  
PEG → Paternally exp gene } may turn off one  
too. → PEG of 15<sup>th</sup> chromosome regulates exp<sup>n</sup> of the allele  
of MES of 14<sup>th</sup> chromosome  
It thus makes the alleles → unreadable  
So deletion of PEG of 15<sup>th</sup>  
chromosome can result in over  
expression of MES 14.

→ Faulty imprinting may cause disorders.  
especially if both the alleles are  
affected. Ex: Obesity, hypertension etc.

→ Species specific, rather high in mammals.  
Only few genes undergo imprinting.

Applications

- Helps to know effect of deletions in diff sexes & variation of diseases according to gender.
- Understand selective inheritance from a particular parent.
- Methylation is used in Genetic Engineering as a cure to stop abnormal gene.
- Ex: we know hereditary glomus tumor is only in PEG. The gene is imprinted in female germline so it is not expressed in offspring of affected mothers.

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## Theories :

① Conflict Theory : By Haiq & Westoby  
to avoid conflict between parental genes during foetal dev.

Ex: Parental Genes → Use all nutrition (growth promoting) for current foetal dev.  
Maternal Genes → Save for next foetus (growth limiting) as well as mother.

② Non-conflict Theory : By Moore ;

To prevent parthenogenesis, where fertilization occurs w/o sperm. Thus Imprinting forces sexual-reproduction.

③ Ovarian Time-Bomb Hypothesis : By Varmusa & Mann

If ovary tries parthenogenesis → Time-Bomb  
Therefore to diffuse it → Imprinting  
(which forces sperm to fuse with ovary)

The genes required to diffuse the time-bomb one present in the sperm.

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## Intersex

[IOM Short note]

Acc. to UN Office of High Commissioner for Human Rights, Intersex people are born with sex characteristics that do not fit typical binary notions of male or female bodies. In some cases the condition is visible at birth but sometimes only becomes apparent in puberty.

The first term for them was coined in early 20<sup>th</sup> century as Hermaphrodites, in biological science

H. is used to describe an organism that can produce both male & female gametes.

Later intersex people were characterised:

① True Hermaphrodites: Presence of both ovarian & testicular tissue. Phenotype depends on which one dominates. It is found that most TH have 46XX karyotype.

② Pseudohermaphrodites: Person whose gonads are consistent with the chromosomal karyotype but whose external genitalia is either ambiguous or at variance with " ". Genitalia develop during 1st 3 months of the gestation period mediated by sex steroids.

a) Female Pst: Have ovaries; 46XX; due to excessive exposure to Androgens invitro (male hormone)

Ex: Excessive Testosterone given to mother during pregnancy is harmful.

b) Male PSH: They have testes but ;  $46XY$   
Genital feminisation observed.

Due to inadequate exposure to Androgen  
 which leads to incomplete dev of the  
 male sexual organs.

yet many simply prefer the term Intersex.  
 In clinical settings, since 2006 "Disorders  
of Sex - Dev" is used.

- Many subjected to cruel operations &  
 sterilizations  $\Rightarrow$  Violation of HR. We  
 need to respect 2013 Malta Declaration  
of Rights of Intersex people by the  
International Intersex Forum (IIF)
- Many consider a term "Hermaphrodite" as  
 misleading as no human can truly be  
 a hermaphrodite.
- Many don't consider 'Intersex' as a  
 disorder hence the scientific term is  
 also contested. Hence "Variations  
of Sex Dev" has been proposed.

→ Anywhere from 0.05 - 1.5% of births are Intersex.

M Psh  $\rightarrow$  Males } but if full feminisation  $\rightarrow$  female  
 G (genital)

F Psh  $\rightarrow$  females }

TH  $\rightarrow$  Male if testes have descended  
 else female.

## Genetic Engineering

- Some say individuals are benefited at the cost of humanity. The preservation of harmful genotypes has resulted in ↑ of GL in man.
- Mutation Rate has ↑ in modern times.
- Synthetic DNA has worked effectively in some lower species of animals.

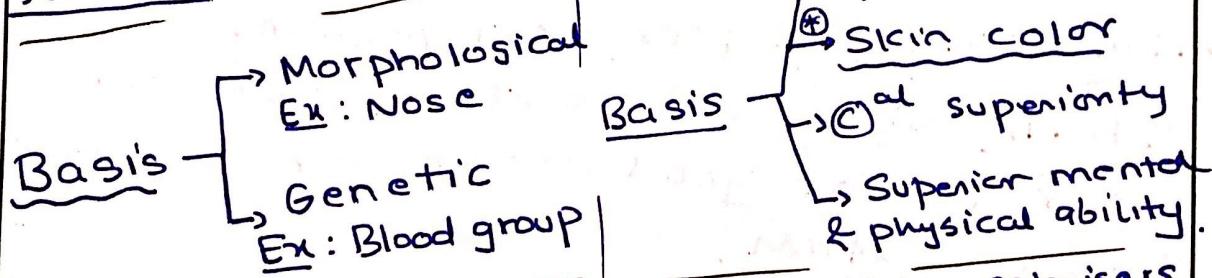
9.5

RaceRace vs Racism [10M]

Acc. to Dobzhansky, Race is a group [m. P.] of populations that share similar gene frequencies. [Race is characterised by its unique gene frequencies.]

Racism on the other hand refers to a belief of superiority & purity of one culture over the others.

Acc. to Franz Boas, Race is strictly a biological concept whereas Racism is a cultural concept.



\* Academic concept to understand human diff. → Leveraged by colonisers to prove their superiority.

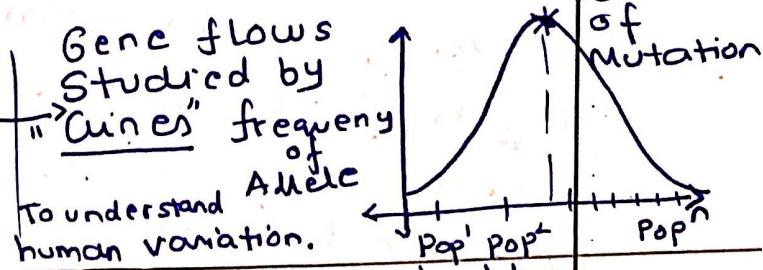
→ Races are usually reproductively isolated

→ Now proven ineffective concept & also a stigmatised one. ① ②

→ Racism also promotes it.

Racism has piggy banked on Race.  
It is a misuse of Race.

Mendelian Pop<sup>n</sup> or Ethnic Group used.



Thus Racial Studies played imp role in the history of Physical Anthropology, in 1800's. Now very discredited.

- Q Is race a valid concept? [Concept of Race]
- No race has exclusive possession of any gene. Flows are very common.
  - Differences between Races might be less than individuals of same race.
  - No agreement on how many genetic differences required for race formation.

good conclusion

⊕ → Lewontin (1971): Studied Races by dividing human populations into 7 geographical zones. He concluded that only 1% of the "differences" were attributable to Race.

→ HGP (2003) 1st Report: All humans share 99.99% of genetic code & remaining 0.01% is not good enough for a racial classification.

studied Race Scientifically & in Totality

→ PostWW2: UNESCO statement on race (1951) was primarily authored by Ashley Montagu: No pure races exist among humans. We are all 1 Homo sapien species. [Race busted]

→ Races don't differ significantly wrt No superior race & No inferior race. their capacities or capabilities. [Racism] → race & [Busted]

→ No harmful effects of inter-racial matings.

A. M. wrote book "Man's most dangerous myth" (1942) about Race & Racism. After this period, A has reduced its interest in Race & also ultimately rejected it. So 'Race Concept' disproven.

Additional Points :

- Blood Group & Race not related:
- Ex: American Indian (T) → 'O'  
Montana (T) → 'A'
- Structural changes in Hb: Due to env & not characteristic of any 1 race. All have same basic structure  $\Rightarrow$  [Hb A].

Why Racism Rejected? 2 WW's fought because of it.

- Still has tremendous hold on Sty, BLM Movt.
- In past, genocide & ethnic cleansing.  
Ex: Holocaust.
- Racism found false by science:
  - ① Industrialised nations of west have better education system hence (T) score.
  - ② Skin color not superiority; but a Glogos Rule reaction to env by melanine content.
  - ③ Negro's due to climate of Africa.
  - ④ Culture & Race are not related. Auer's Rule
- Rise of Cultural Relativism in Anthropology
- Note: Thomson's Rule & humidification of air.

How to reduce:  $1^{\circ} + 2^{\circ} S \rightarrow$  Reduces "fear of unknown".

Racism? ✓ Textbooks/Education  
✓ Greater Interaction

Bergman's Rule  
Thomson's Rule

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①

②

Q How are races formed? Role of Env & Heredity?

Start in the modern way S.D.  
Ashley Montagu defined Race in similar was as Dobzhansky.

Thus Race formation requires change in gene frequencies which in humans only occurs via microevolutionary processes.

Elaborate ⑤ in brief; draw diagram  $\Rightarrow$  Race formation.

a) Mutations: Meaningful ones in humans are caused by radiation which is environmental.

b) NS: Environmental; by itself natural

c) I, Hy & GD: Cultural factors; which is man-made part of env; hence these are also environmental.

$\therefore$  All 5 ME factors which change the gene frequencies are environmental only. Thus Role of env is understood in terms of M.E. ✓

Now heredity passes traits to subsequent generation in its purest form. If it were to only continue like this, then there would have been no change in gene frequencies & hence no race formation.

Since env is dynamic; heredity has to change itself to suit the needs of the env. This interaction leads to the formation of Races. Env compels heredity to result in race formation.

Ex: HbA/Hbs  $\rightarrow$  Mediterranean (env).

Ex: Long env process: High altitude/latitude.

Ex: Cultural influences: If eat maize a lot  $\rightarrow$  B3(vitamin) deficiency

Ex: Cultural influences: If eat maize a lot  $\rightarrow$  B3(vitamin) deficiency

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## Q) Race & Racial Classifications [20M]

Race has 2 definitions

### Pre-Mendelian

→ Differences in terms of certain physical features.  
Ex: Small feet of Chinese.

\* Thus there are 2 types of Racial Criteria

### Modern Era

→ Group that has certain gene frequencies.

Basis of Racial Classification

### Morphological [15M Each]

continuous outer appearance

#### Morphoscopic (Somatoscopic)

Ex: Skin color  
→ Eye color & shape  
→ Hair color & texture, form  
→ Build

#### Morphometric

Ex: Nasal Index  
→ Cranial Index  
→ Facial Index  
→ Stature

### Genetic [15M Each]

discrete  
(Monogenic)  
(Polygenic)

→ Blood groups  
→ HLA, Hb, Hp, GM → Enzymes  
→ Proteins  
→ Faster  
→ Secretor  
→ Y-chromosome

→ Dermatoglyphics  
→ Chromosomal variation

### CONCLUSION: (Genetic)

Acc. to W.C Boyd for any criteria to work:  
→ Mendelian Principle of Inheritance / Known inheritance.

→ Discrete & non-continuous.

→ Preferably hereditary.

→ Compared with Boyd  
→ Not easily influenced by env, & stable.

Not known also

→ Arise quite early in human evolution.

→ Must not be susceptible to much individual variation.

Hereditability quite complex

Thus most of morphological criteria don't meet these conditions. Most genetic

Adaptive easily influenced by env.

Criteria do satisfy. But pure races don't exist in humans (UNESCO: 1951).

Climate, Nutrition & Pollution.

Therefore racial classifications have very limited utility & slowly being abandoned.



## Morphological Criteria

① Hooton [American AP] in 1947 classified the world's pop<sup>n</sup> into '3 Races' based on morphological criteria  $\Rightarrow$  C, M & Negroid.

	Caucasoid	Mongoloid	Negroid
① Skin color	Leucoderm (white)	Xanthoderm (yellow)	Melanoderm (black)
② Hair Form	wavy; cymotrichy	Smooth; leiotrichy	Wolly; Volutrichy
③ Hair texture	fine; $< 60$ micron	Medium; 60-80	coarse; $> 80$
④ Hair color	Blonde	Brown	Black
⑤ Eye Shape	(open & straight)	Narrow; epicanthic fold	(open & straight)
⑥ Eye Color	Blue - light brown No blue pigment, If on only 1 side of eye pigment there	Light - Dark brown green pigment as such exists Blue color eye; if both $\Rightarrow$ Brown (behind)	Brown - Black Brown - Black (behind & ahead)
⑦ Build	Linear	Lateral $>$ Linear	Lateral
Biparietal occipito-frontal distance			
Geophilic Index			
earliest & most common criteria Brachy; $> 0.81$ Face may/may not match head: Harmonic / conditions Dolico; $< 0.76$ Disharmonic			
② Nasal Index $\left[ \frac{b}{l} \times 100 \right] *$	Leptorrhine $< 70$ Bridge is high	Mesorrhine [70 - 85] Bridge is medium	Platyrhine 785 Bridge is low.
③ Facial Index $\left[ \frac{l}{b} \times 100 \right]$	Europoscopic $< 84$	Mesoprosopic [84 - 88]	Leptoprosopic $> 88$
④ Stature AC Haddon's scale	Pigmy $\rightarrow$ Short $\rightarrow$ Med $\rightarrow$ tall $\rightarrow$ very tall $< 148\text{cm}$ 148-158      158-168      168-172 $> 172\text{cm}$		

②  
3  
Morphological  
Criteria

②  
Morphology

Serological Criteria

ABO; Rh  
Hb in 9.6.  
G6PD  
Gm

From the above table it is not possible even to draw broad generalizations. However, we realise Genes are not distributed acc. to Races. Genes are distributed acc. to geographical needs & as directed by Natural selection.

Non-Serological Criteria

can be  $[p+q=1]$   
represented by a  
bar diagram.

T	t
100	0
75	25
50	50
25	75
0	100

① Taster/Non-Taster: Negroid  $\Rightarrow tt$ ,  
Caucasoid  $\Rightarrow Tt$ ,  
2. Mongoloid

② Secretor Status: Sweat, Tears, Semen  $\Rightarrow$  contain Antigen S  
Contain a blood group like substance  
 $SS/Ss(V); ss(X)$ , Same as Taster is  
\* Secretor Variation

③ Length of Y Chromosome: Found by 'Q' staining.  
Mongoloid  $\rightarrow$  Longer; Negroid  $\rightarrow$  Shorter

Cummins &  
Middle, 1931

④ Dermatoglyphics: Study of dermal ridge  
lines on finger, palm, toes & soles.

Parameters like total ridge count, main line index & Hypothenar ridge count are used to Thener ridge count one used to classify human populations into diff races.

$\Rightarrow$  They do not change with age & are a Polygenic trait.

Whorls  $\rightarrow$  Mongoloid  
Loops  $\rightarrow$  Caucasoid  
Arches  $\rightarrow$  Negroid

Distribution  
Usually

diff  
ridg.  
count  
Pattern  
intensity  
Index

Furukawa Index  
Whorl denkmajer Index

This skin diff  
from skin elsewhere  
Serves as 6<sup>th</sup> group