LETHAL GENES

- Genes which result in the reduction of viability of an individual or become a cause for death of individuals carrying them are called as lethal genes.
- Certain genes are absolutely essential for survival. Mutation in these genes creates lethal allele.

- Lethal genes were first discovered by Lucien Cuénot while studying the inheritance of coat colour in mice.

- He expected a phenotype ratio from a cross of 3 yellow:1 white, but the observed ratio was 2:1.

TYPES OF LETHAL ALLELES

Lethal alleles fall into four categories.

1. **Early onset-** lethal alleles which result in death of an organism at early stage of life, for example, during embryogenesis.

2. **Late onset-** lethal allele which kills organism at their final stage of life are known as late onset allele.

3. **Conditional-** lethal allele which kill an organism under certain environmental conditions only.

   e.g., some temperature sensitive alleles kill organisms only at high temperature.

4. **Semi lethal** – Lethal allele which kill only some individuals of the population but not all are know as semi lethal.

- Lethal alleles are dominant or recessive.

- Fully dominant lethal allele kills organism in both homozygous and heterozygous condition.

- Recessive lethal alleles kills organisms in homozygous condition only.

DOMINANT LETHAL GENES

- Dominant lethal allele kills both in homozygous and heterozygous states.
- Individuals with a dominant lethal allele die before they can leave progeny.
- Therefore, the mutant dominant lethal is removed from the population in the same generation in which it arose.

EXAMPLES OF DOMINANT LETHAL ALLELES

- An example is the "creeper" allele in chickens, which causes the legs to be short and stunted.
- Creeper is a dominant gene, heterozygous chickens display the creeper phenotype.
- If two creeper chickens are crossed, one would expect to have (from Mendelian genetics) 3/4 of the offspring to be creeper and 1/4 to be normal.
- Instead the ratio obtained is 2/3 creeper and 1/3 normal.
- This occurs because homozygous creeper chickens die.

	P	p
P	PP lethal	Pp creeper
p	Pp creeper	pp normal

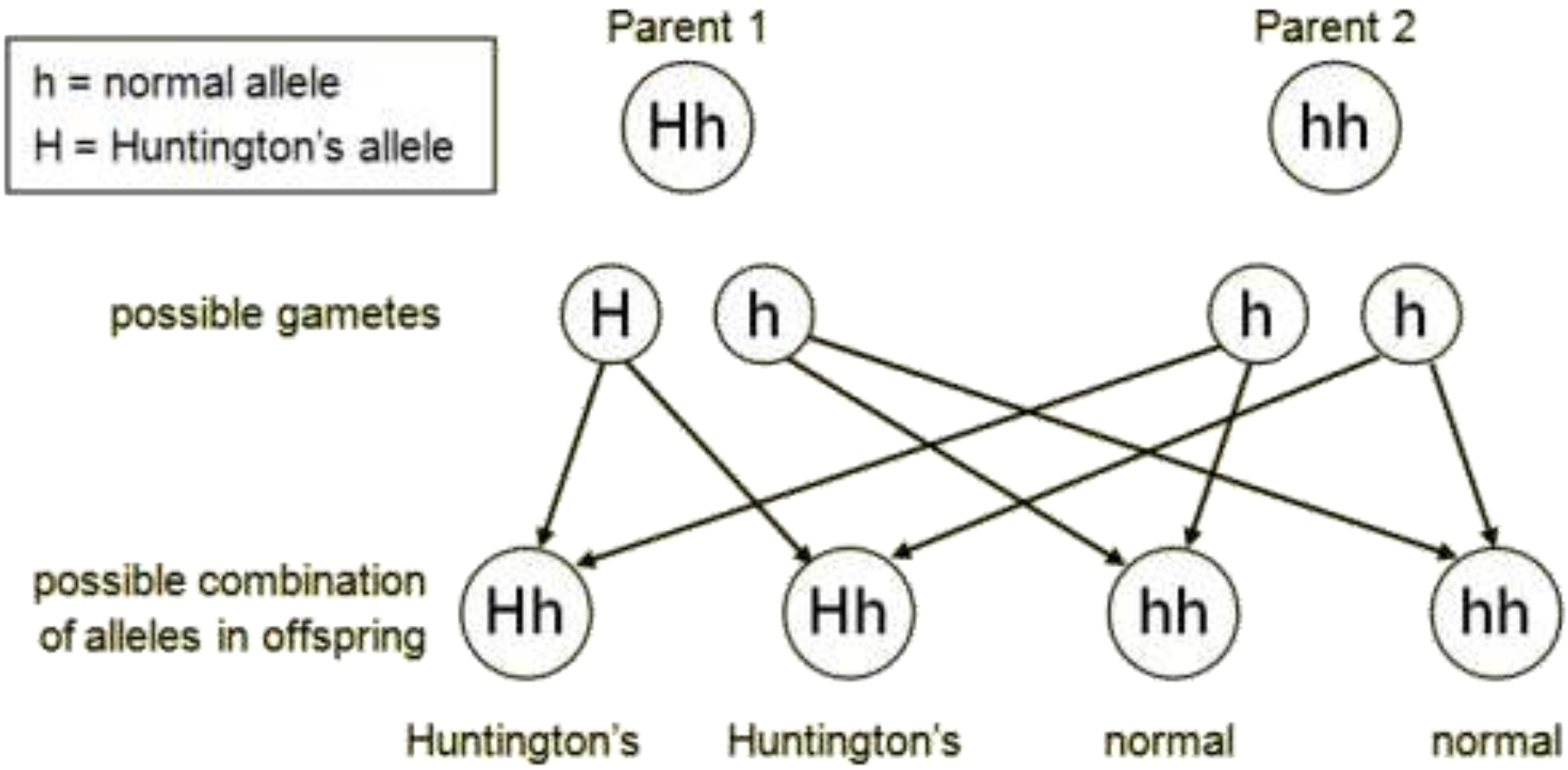
HUNTINGTON'S DISEASE

- Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).

- Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties.

- Mutations in the *HTT* gene cause Huntington disease. The *HTT* gene provides instructions for making a protein called huntingtin.
- HH → Individual dies of Huntington's disease
- Hh → Individual dies of Huntington's disease
- hh → Normal individual

- Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions.
- Affected individuals may have trouble walking, speaking, and swallowing.
- Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin.


h = normal allele
H = Huntington's allele
Parent 1
Hh
Parent 2
hh
possible gametes
H
h
h
h
possible combination of alleles in offspring
Hh
Hh
hh
hh
Huntington's
Huntington's
normal
normal

RECESSIVE LETHAL GENES

Recessive lethal genes kill only when they are in homozygous state. They may be of two kinds:

- one which has no obvious phenotypic effect in heterozygotes.
- one which exhibits a distinctive phenotype when heterozygous.

EXAMPLES OF RECESSIVE LETHAL ALLELLES

- **Brachydactyly** –

➢ A genetic state in which the fingers are unusually short in heterozygotic condition. But, this condition is lethal during early years to homozygous recessive individuals due to major skeletal defects.

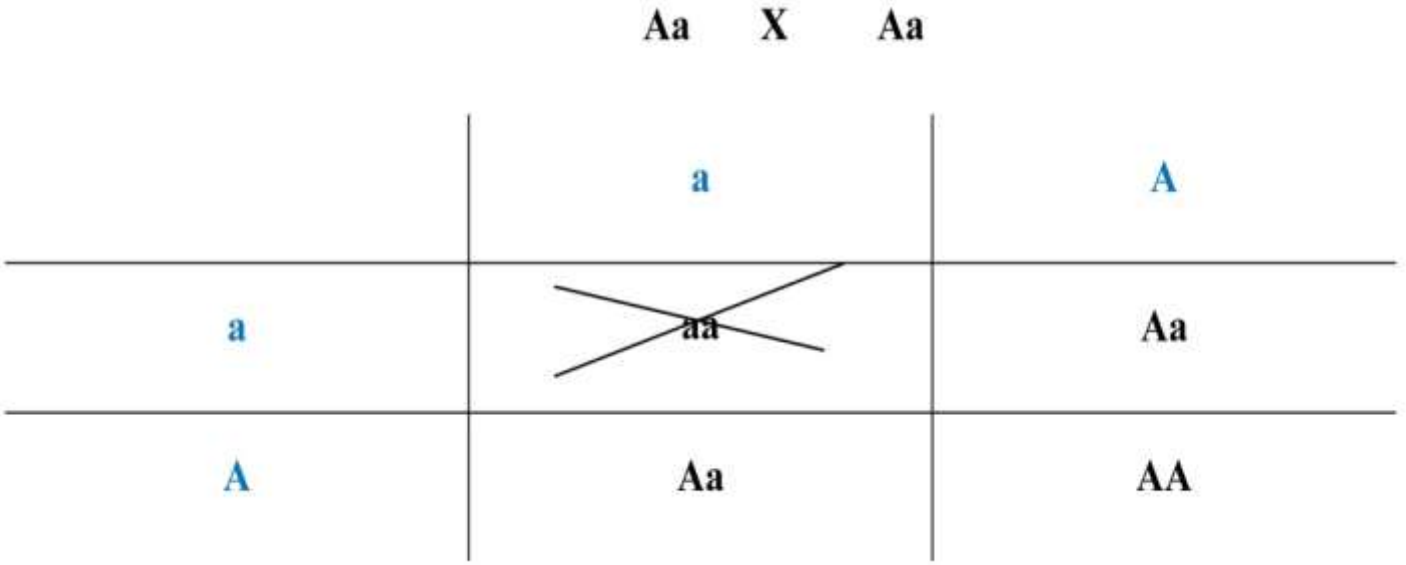
➢ Most surgeries for brachydactyly are cosmetic.

➢ Some therapy might be needed to help with kinesthetic activities.

What causes Brachydactyly?

- A mutation occurs in IHH gene which encodes proteins responsible for bone growth and differentiation.
- When a single mutated copy of the allele is present, the phenotype has just few deformations of skeletal bones. This is because one dose of functional IHH allele is almost enough to produce a required amount of a protein essential for a skeletal formation.
- If an organism inherits two mutated copies of IHH allele no protein essential for skeletal bones formation is produced and development of embryo cannot be continued - the embryo dies.

Let's say that an allele **a** is recessive and codes for a completely dysfunctional form of a protein essential for bone growth, and **A** is a dominant wild type allele. If heterozygotes for these alleles procreate, then:




a

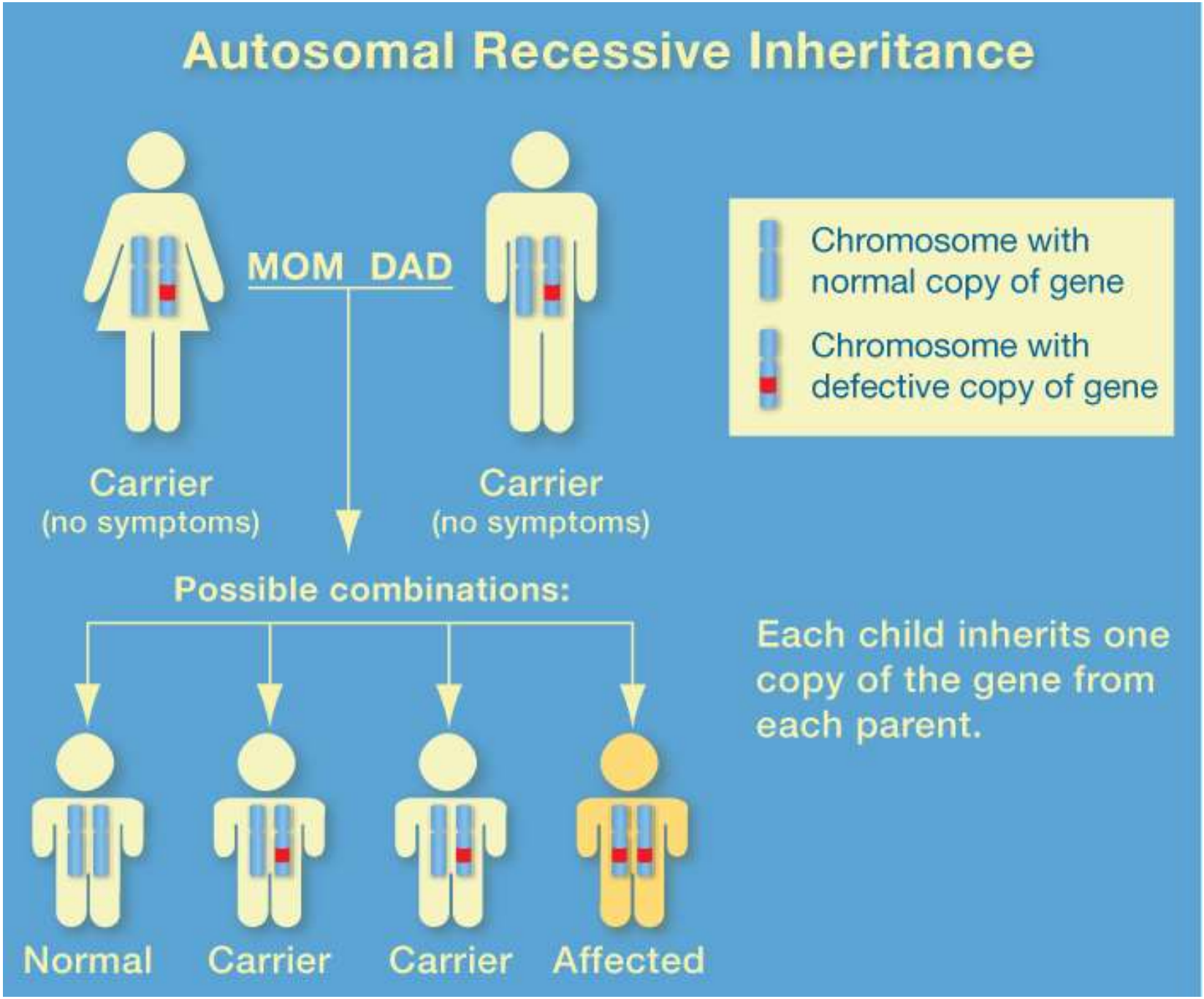
Sickle Cell Anemia –

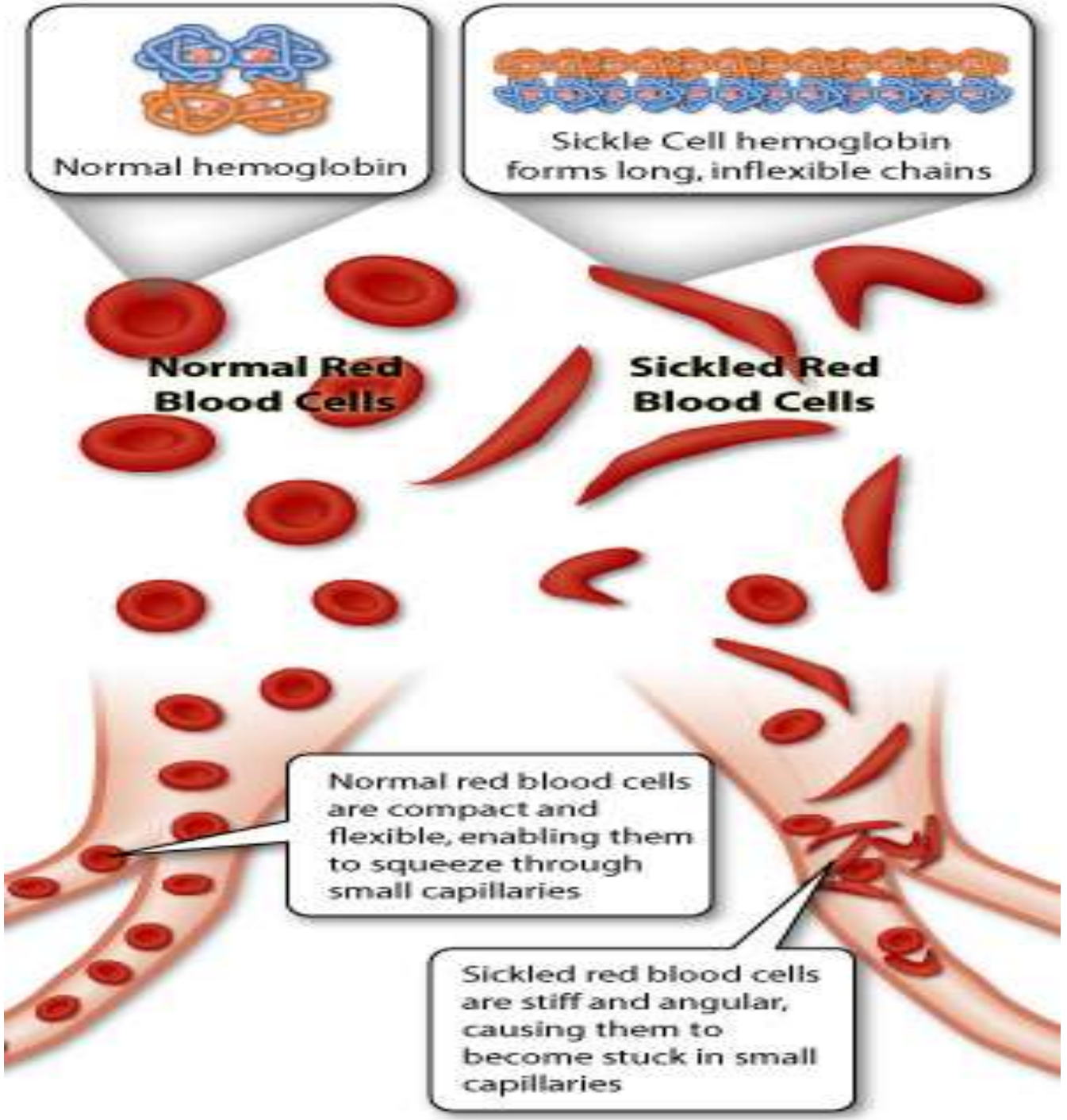
- A genetic state that is often fatal in the homozygous recessive condition.
- People who inherit one good copy of the gene and one mutated copy are carriers. They are clinically normal, but can still pass the defective gene to their children.
- When sickle-shaped red blood cells get stuck in blood vessels, patients can have episodes of pain called crises. Other symptoms include delayed growth, strokes, and jaundice (yellowish skin and eyes because of liver damage).

Genetics of Sickle Cell Anemia

Genotypes	Phenotypes
Hb^NHb^N	Normal haemoglobin
Hb^NHb^S	Sickle cell trait
Hb^SHb^S	Sickle cell anaemia

Animation showing sickle cells


Autosomal Recessive Inheritance
MOM
DAD
Carrier
(no symptoms)
Carrier
(no symptoms)
Chromosome with normal copy of gene
Chromosome with defective copy of gene
Possible combinations:
Each child inherits one copy of the gene from each parent.
Normal
Carrier
Carrier
Affected

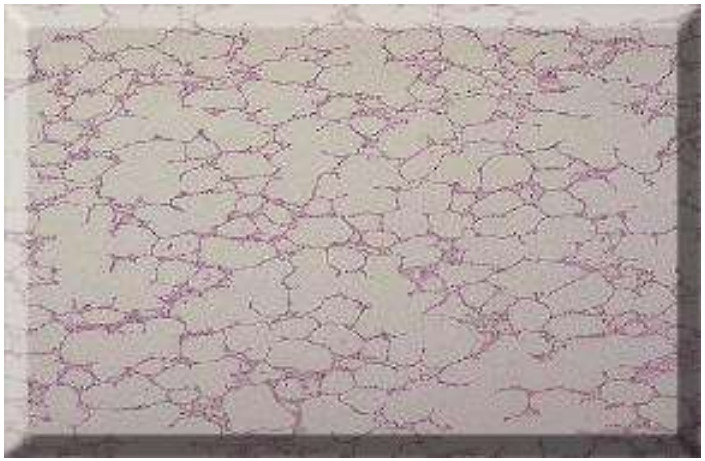

Normal hemoglobin
Sickle Cell hemoglobin forms long, inflexible chains
Normal Red Blood Cells
Sickled Red Blood Cells
Normal red blood cells are compact and flexible, enabling them to squeeze through small capillaries
Sickled red blood cells are stiff and angular, causing them to become stuck in small capillaries

Cystic Fibrosis

- A genetic state that is fatal to every homozygous recessive person by age 30.
- Sticky mucus accumulates in the lungs giving rise to constant and risky respiratory infections.
- It is caused due to malfunctioning of chloride ion channels in ducts.

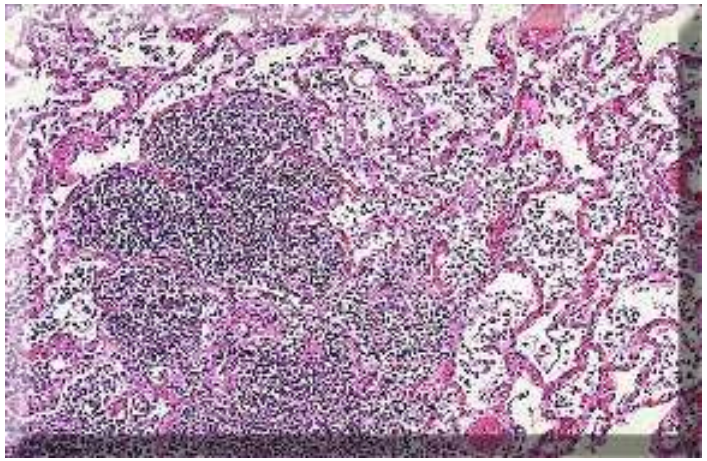
Lungs in cystic fibrosis

Normal lung



Normal alveolar appearance

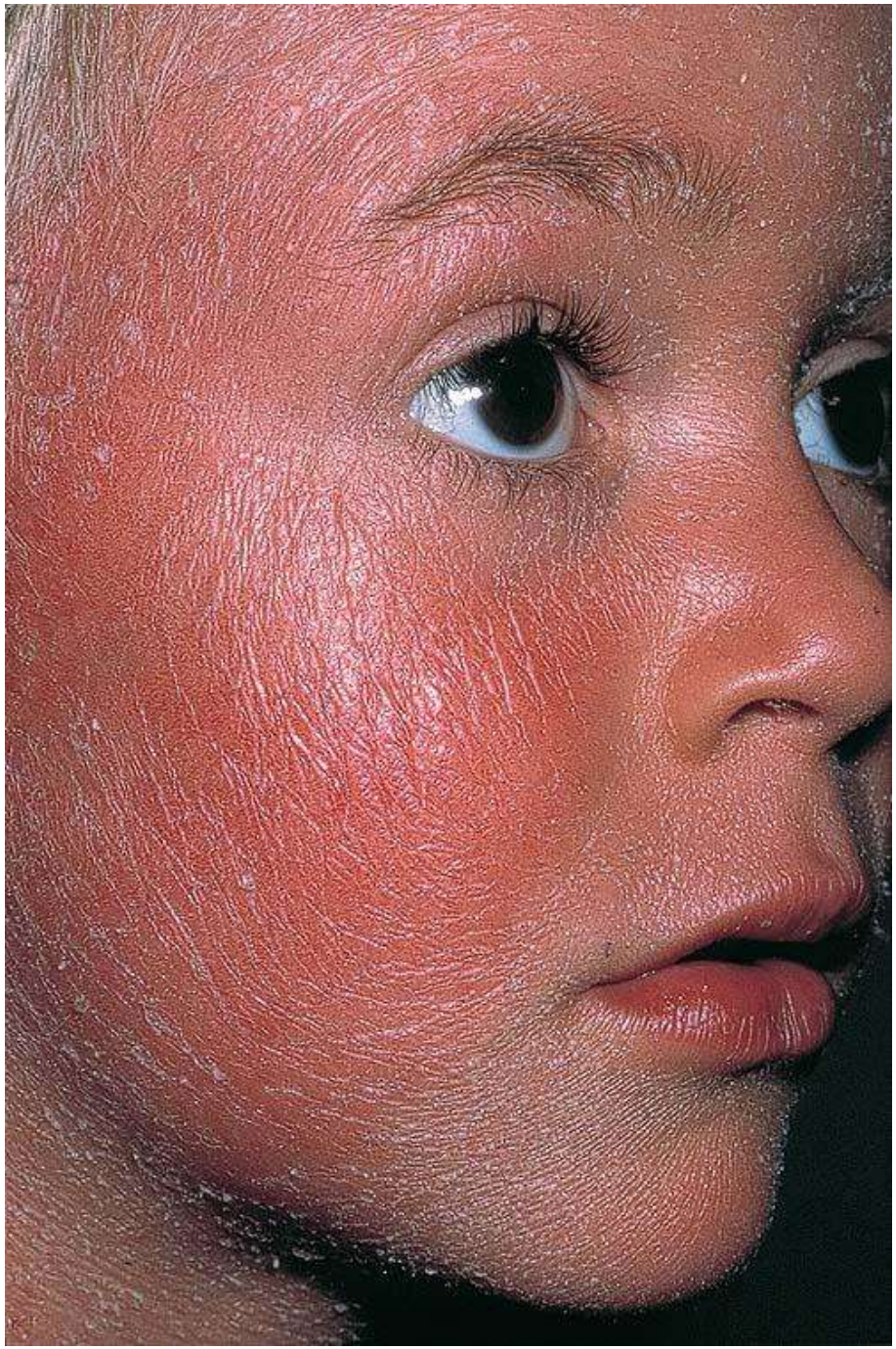
CF lung



Dilated crypts
filled with mucus and bacteria.

Congenital Ichthyosis

- Children with this disease are born with crusted leathery skin with deep splits.
- These splits lead to bleeding, infection and death.
- In Ichthyosis, the skin's natural shedding process is slowed or inhibited and in some types, skin cells are produced too rapidly.
- Most types of autosomal recessive congenital ichthyosis require two forms of treatment - a reduction in the amount of scale buildup and moisturising of the underlying skin.




https://derm.s.net

COAT COLOUR IN MICE

- The coat colour of mice is governed by a multiple allelic series in which A allele determines *agouti,* A^Y allele determines *yellow* coat and a allele forms *black* coat.
- The dominance hierarchy is as follows:

$$A^Y > A > a$$

The A^Y allele acts as recessive lethal, since in the homozygous state ($A^Y A^Y$), it kills the individual in early embryonic state.

Thus, when two yellow coated heterozygotes (A^Y A) are crossed, they produce a progeny showing a ratio of 2:1 since homozygous yellow individuals (A^Y A^Y) are never born due to lethal effect of AY gene.