Genetic Disorders

Dr. Gary Mumaugh

Brief History

- First there was Gregor Mendel, a monk who studied inherited characteristics.
- This was followed by Francis crick and James Watson who unraveled the DNA molecule.
- This has led us to understanding the human genome sequence.

Gregor Mendel - 1866

Gregor Mendel

- Gregor Mendel published the results of his investigations of the inheritance of "factors" in pea plants.

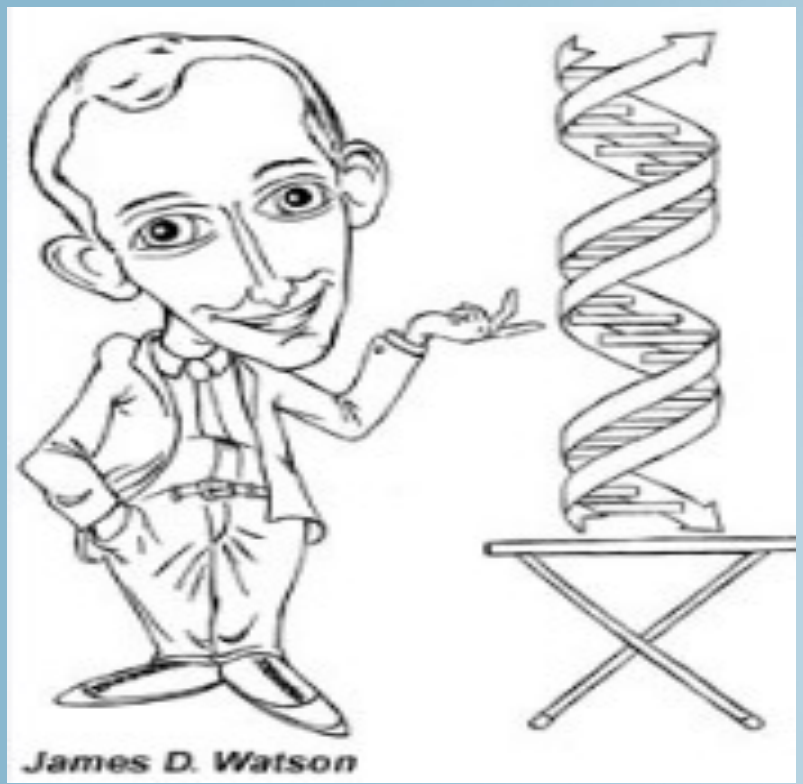
Rosalind Franklin - 1950s

Rosalind Franklin

- Maurice Wilkins, Rosalind Franklin, Francis H. C. Crick of Britain and James D. Watson of the U.S. Discover chemical structure of DNA, starting a new branch of science - molecular biology.

Watson and Crick

- Watson and Crick made a model of the DNA molecule and proved that genes determine heredity



Arthur Kornberg

Arthur Kornberg

- 1957 - of the U.S.
- produced DNA in a test tube.

Genetic Code - 1966

- The Genetic code was discovered; scientists are now able to predict characteristics by studying DNA.
- This leads to genetic engineering, genetic counseling.

	U	C	A	G
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys
	UUA Leu	UCA Ser	UAA End	UGA End
	UUG Leu	UCG Ser	UAG End	UGG Trp
C	CUU Leu	CCU Pro	CAU His	CGU Arg
	CUC Leu	CCC Pro	CAC His	CGC Arg
	CUA Leu	CCA Pro	CAA Gln	CGA Arg
	CUG Leu	CCG Pro	CAG Gln	CGG Arg
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser
	AUC Ile	ACC Thr	AAC Asn	AGC Ser
	AUA Ile	ACA Thr	AAA Lys	AGA Arg
	AUG Met	ACG Thr	AAG Lys	AGG Arg
G	GUU Val	GCU Ala	GAU Asp	GGU Gly
	GUC Val	GCC Ala	GAC Asp	GGC Gly
	GUA Val	GCA Ala	GAA Glu	GGA Gly
	GUG Val	GCG Ala	GAG Glu	GGG Gly

Genetic Code

Barbara McClintock

- Barbara McClintock of the U.S. was awarded the Nobel Prize (1983) for her discovery that genes are able to change position on chromosomes.

DNA Fingerprinting - late 1980's

- An international team of scientists began the project to map the human genome.
- The first crime conviction based on DNA fingerprinting, in Portland Oregon.

Gene Therapy - 1990

- Gene therapy was used on patients for the first time.

DNA Testing - 1995

- DNA testing in forensics cases gains fame in the O.J. Simpson trial

Cloning Begins - 1997

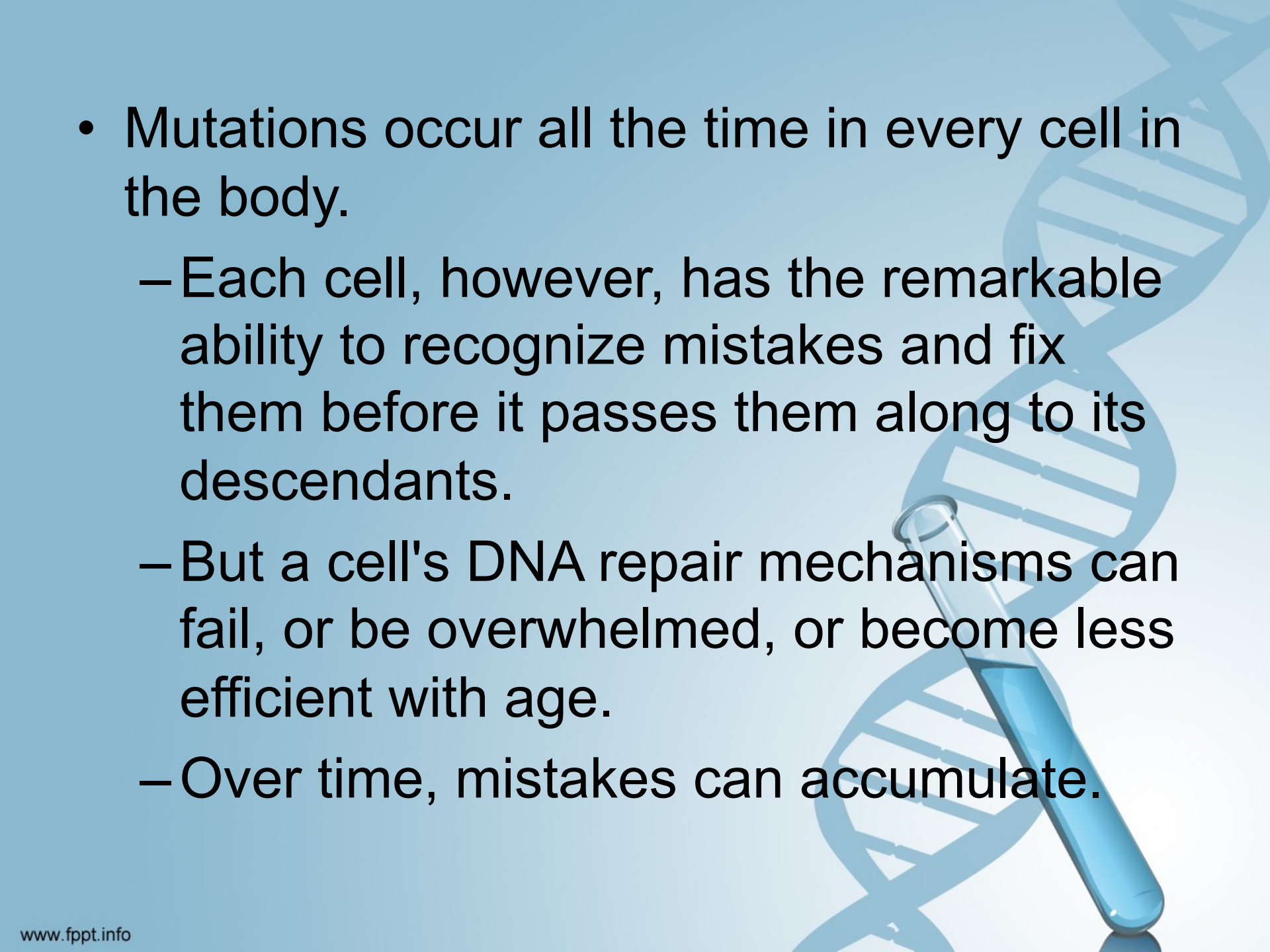
- Dolly the sheep - the first adult animal clone.


otd
On This Day

Mutations

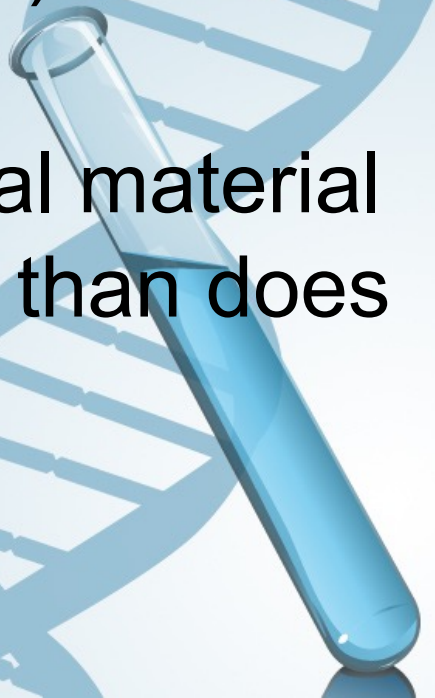
- Gene mutations can be either inherited from a parent or acquired.
- A hereditary mutation is a mistake that is present in the DNA of virtually all body cells.
  - Hereditary mutations are also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn.

- Mutations occur all the time in every cell in the body.
  - Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants.
  - But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age.
  - Over time, mistakes can accumulate.



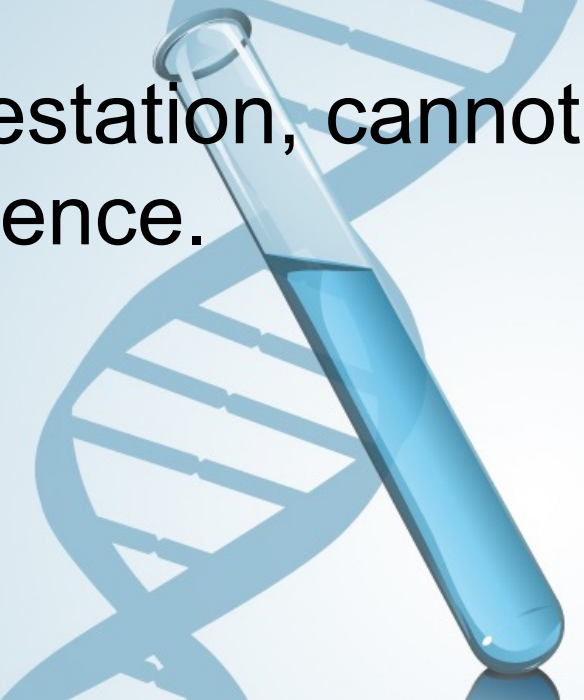
General Features of Chromosomal Disorders

- May be caused by absence (deletion, monosomy), excess (trisomy), or abnormal rearrangements (translocations) of chromosomes.
- In general, loss of chromosomal material produces more severe defects than does gain of chromosomal material.



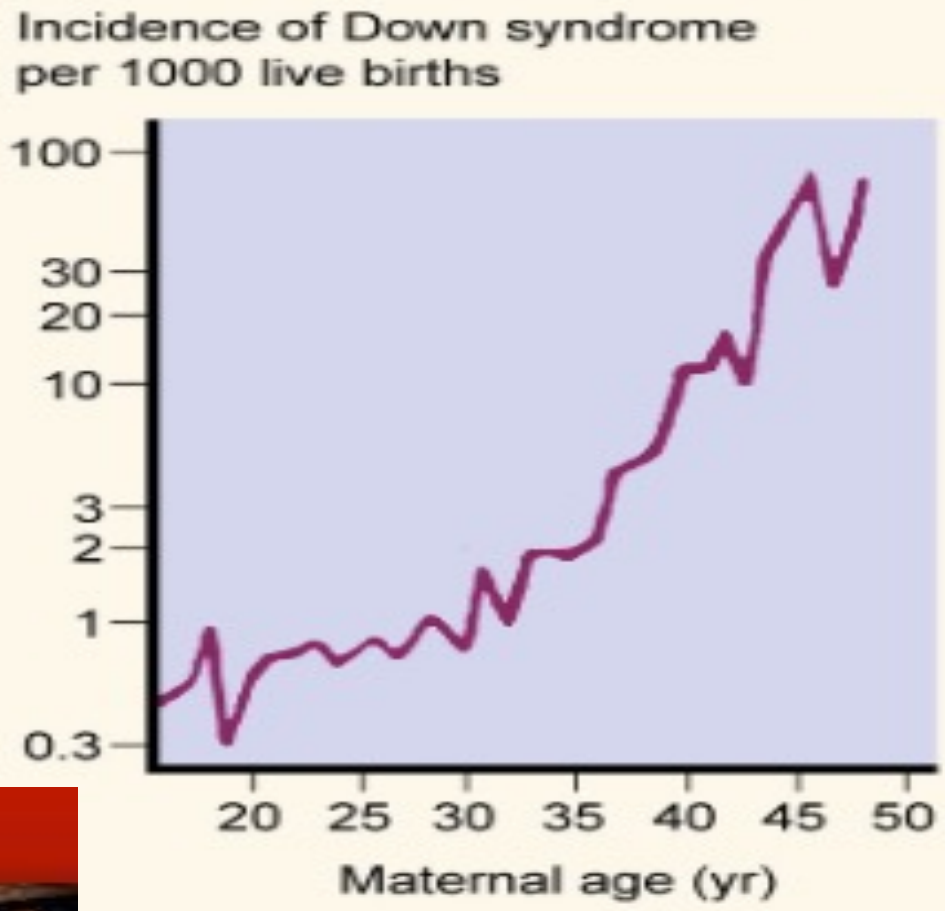
General Features of Chromosomal Disorders

- Sex chromosomal disorders often produce subtle abnormalities, sometimes not detected at birth.
- Infertility, a common manifestation, cannot be diagnosed until adolescence.

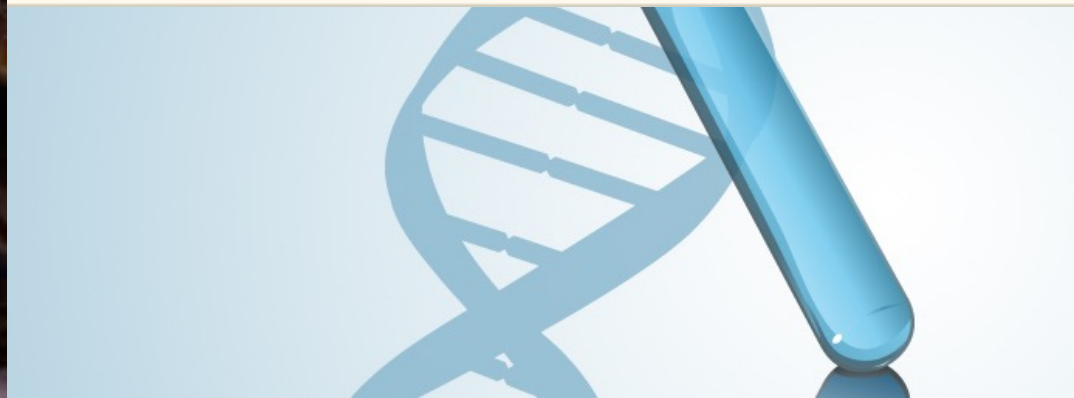


Down's Syndrome (Trisomony 21)

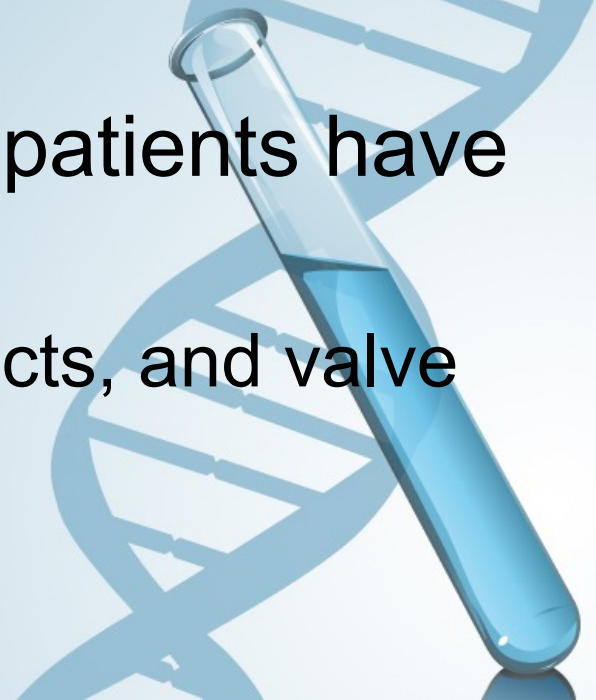
- Is the most common of the chromosomal disorders.
- Caused by non-disjunction of the 21st chromosome.
- Maternal age has a strong influence on the incidence of Down syndrome.
  - It occurs in 1 in 1550 live births in women younger than 20 years, in contrast with 1 in 25 live births in women older than 45 years.


Incidence of Down syndrome
per 1000 live births
100
30
20
10
3
2
1
0.3
20
25
30
35
40
45
50
Maternal age (yr)


Newsweek



- Is a leading cause of severe mental retardation; approximately 80% of those afflicted have an IQ of 25 to 50. Ironically, these severely disadvantaged children may have a gentle, shy manner and may be more easily directed than their more fortunate normal siblings.
- Approximately 40% of the patients have congenital heart disease
  - Most commonly septal defects, and valve malformations

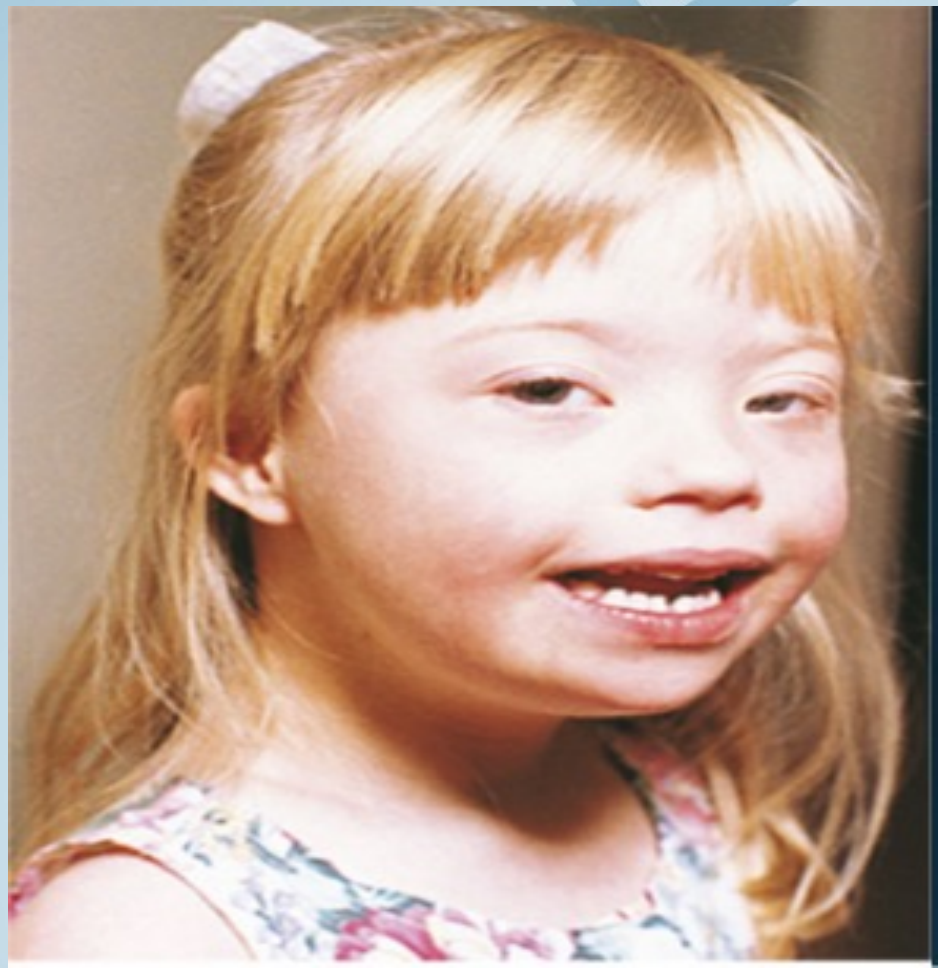


- Children with trisomy 21 have a 10- to 20-fold increased risk of developing acute leukemia.
- Virtually all patients with trisomy 21 older than age 40 develop neuropathologic changes characteristic of Alzheimer disease.
- Patients with Down syndrome demonstrate abnormal immune responses that predispose them to serious infections.

Life Expectancy

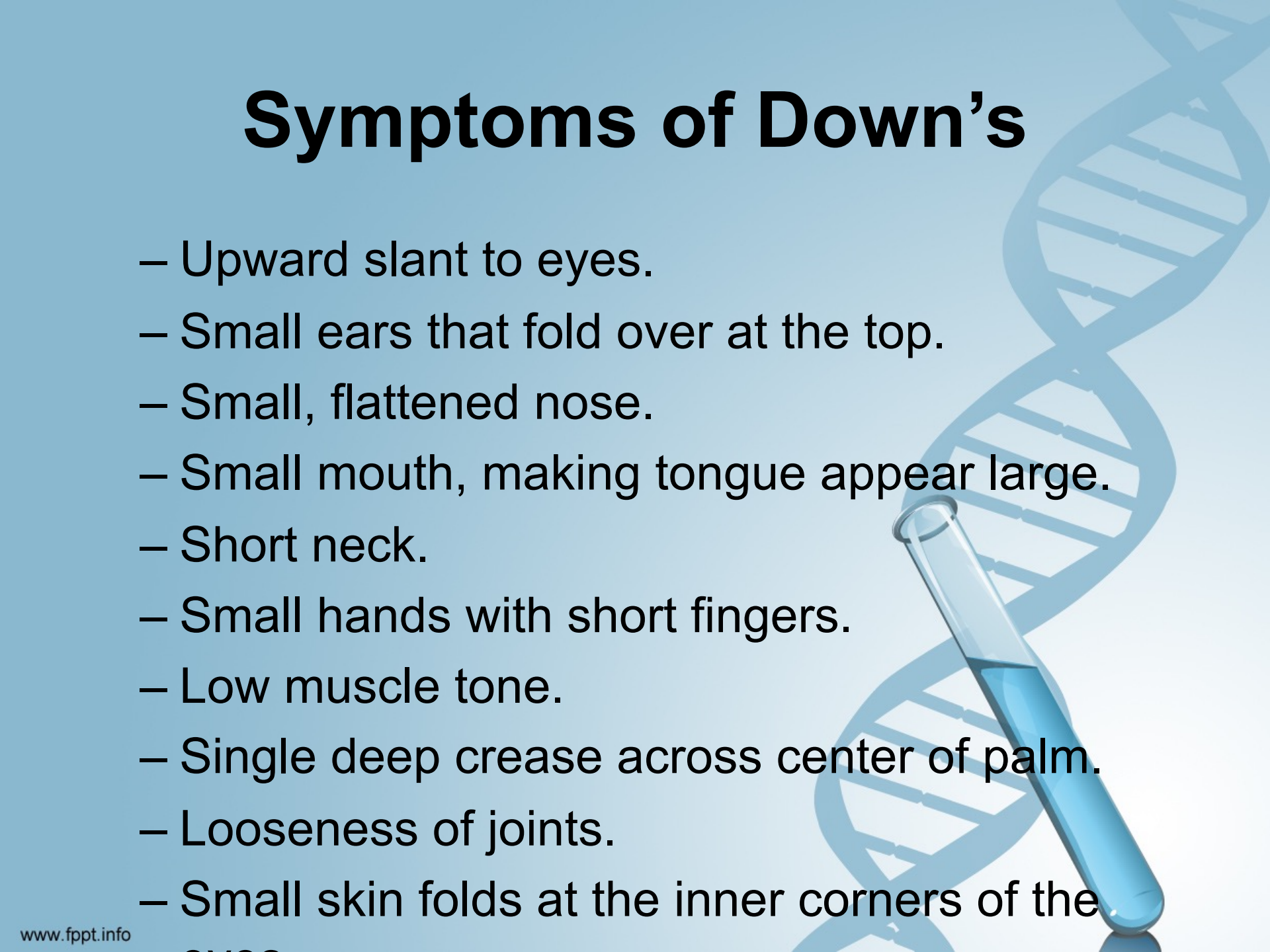
- Today the average lifespan of a person with Down syndrome is approximately 60 years.
- As recently as 1983, the average lifespan of a person with Down syndrome was 25 years.
- The dramatic increase to 60 years is largely due to the end of the inhumane practice of institutionalizing people with Down syndrome.

The diagnostic clinical features of this condition - flat facial profile, oblique palpebral fissures, and epicanthic folds - are usually readily evident at birth.



Symptoms of Down's

- Upward slant to eyes.
- Small ears that fold over at the top.
- Small, flattened nose.
- Small mouth, making tongue appear large.
- Short neck.
- Small hands with short fingers.
- Low muscle tone.
- Single deep crease across center of palm.
- Looseness of joints.
- Small skin folds at the inner corners of the

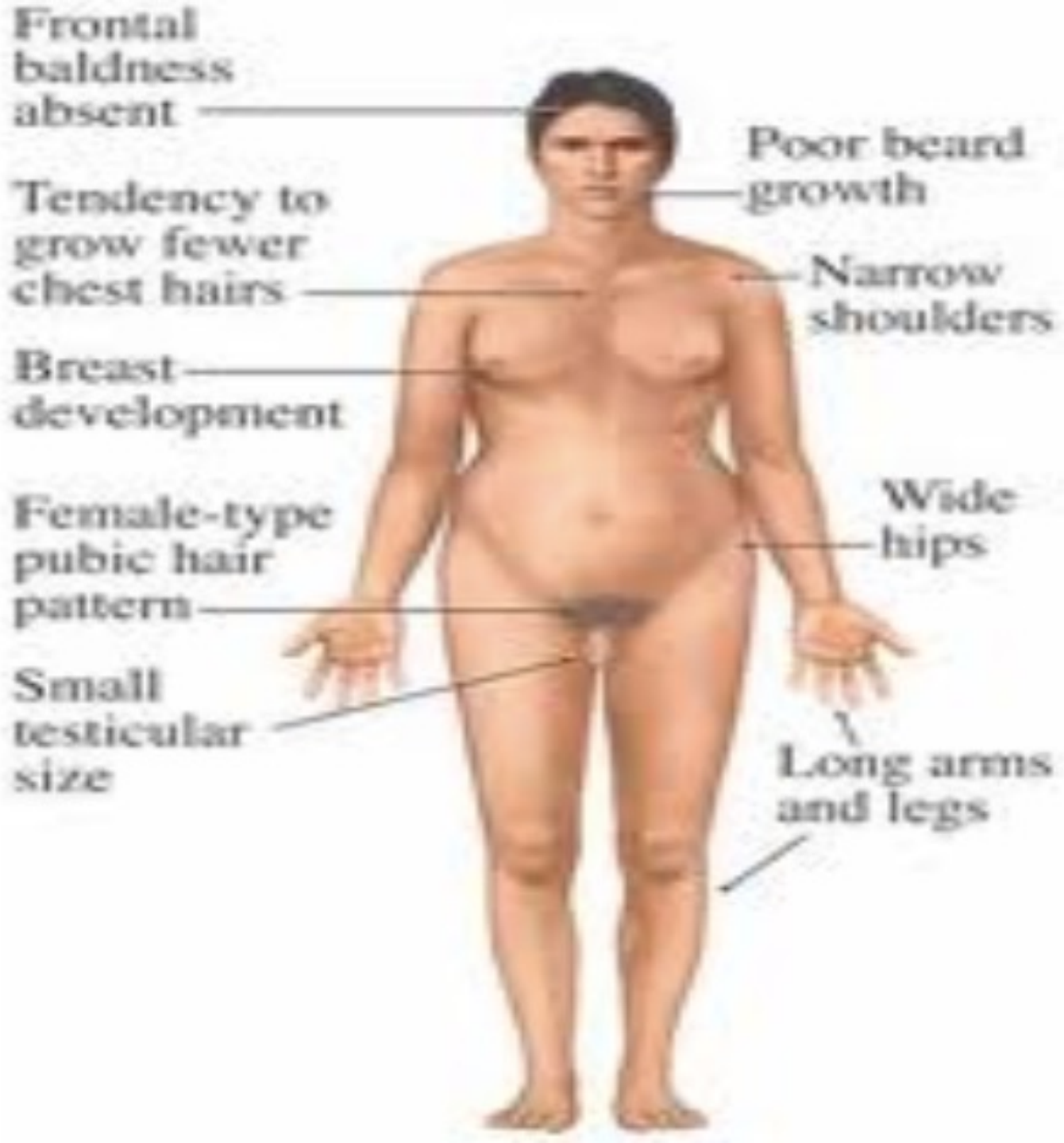


Symptoms of Down's

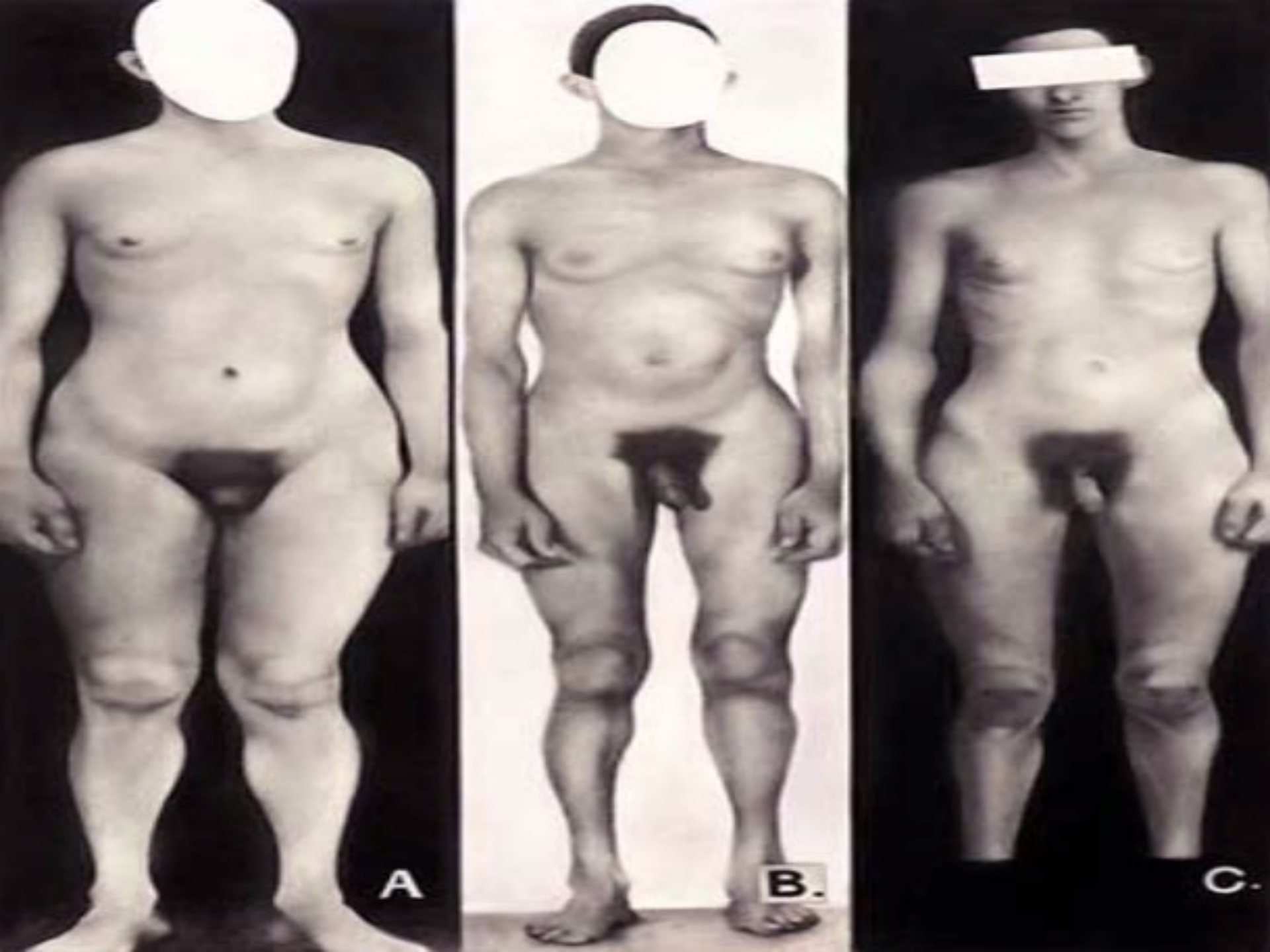
- Single deep crease across center of palm.
- Looseness of joints.
- Small skin folds at the inner corners of the eyes.
- Excessive space between first and second toe.
- In addition, down syndrome always involves some degree of mental retardation, from mild to severe. In most cases, the mental retardation is mild to moderate.

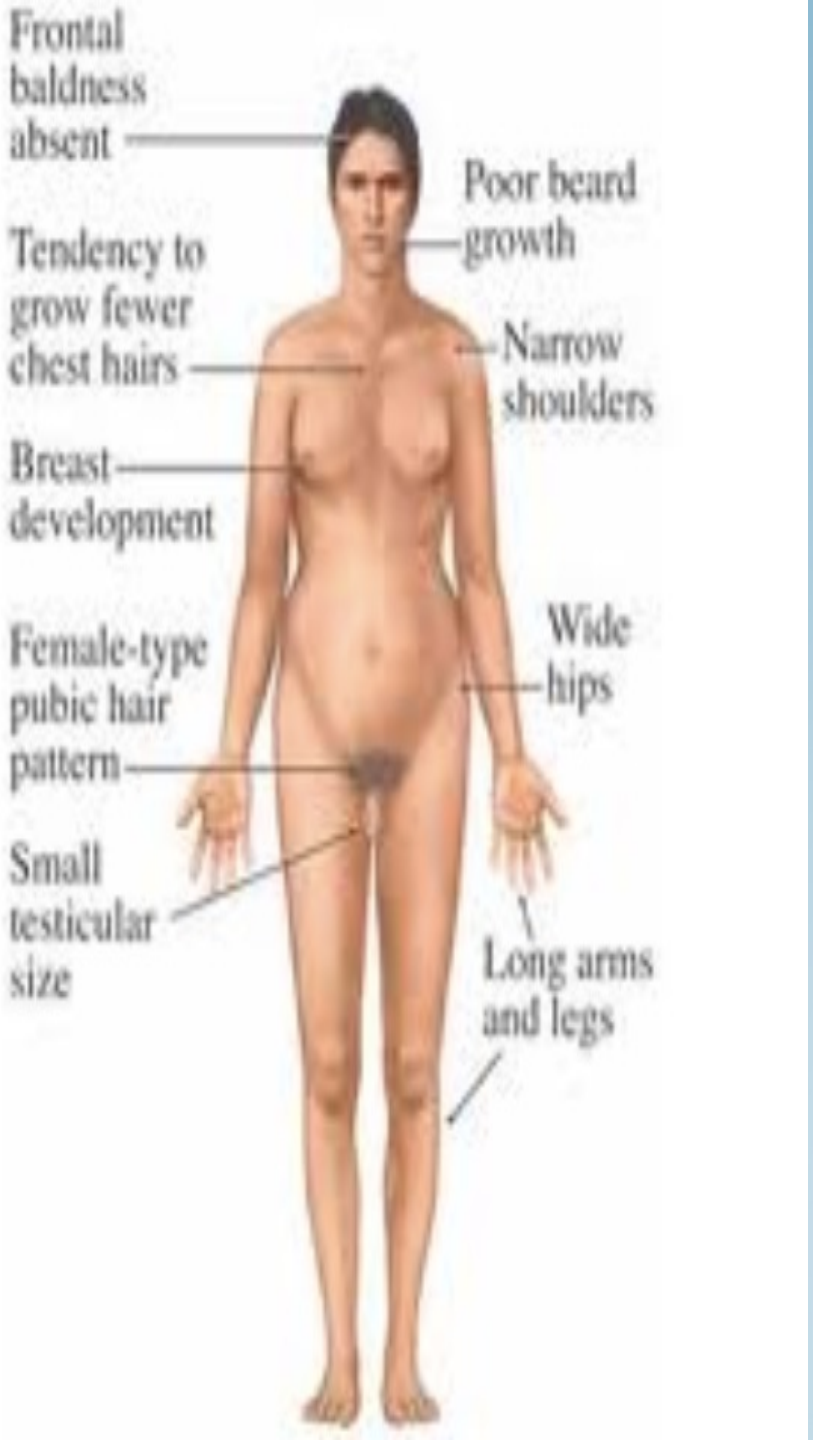
Kleinfelter's Syndrome

- Is best defined as male hypogonadism that develops when there are at least two X chromosomes and one or more Y chromosomes.
- The Sperm containing both X and Y combines with an egg containing the X, results in a male child. The egg may contribute the extra X chromosome.


Frontal baldness absent
Tendency to grow fewer chest hairs
Breast development
Female-type pubic hair pattern
Small testicular size
Poor beard growth
Narrow shoulders
Wide hips
Long arms and legs

- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present


A
B.
C.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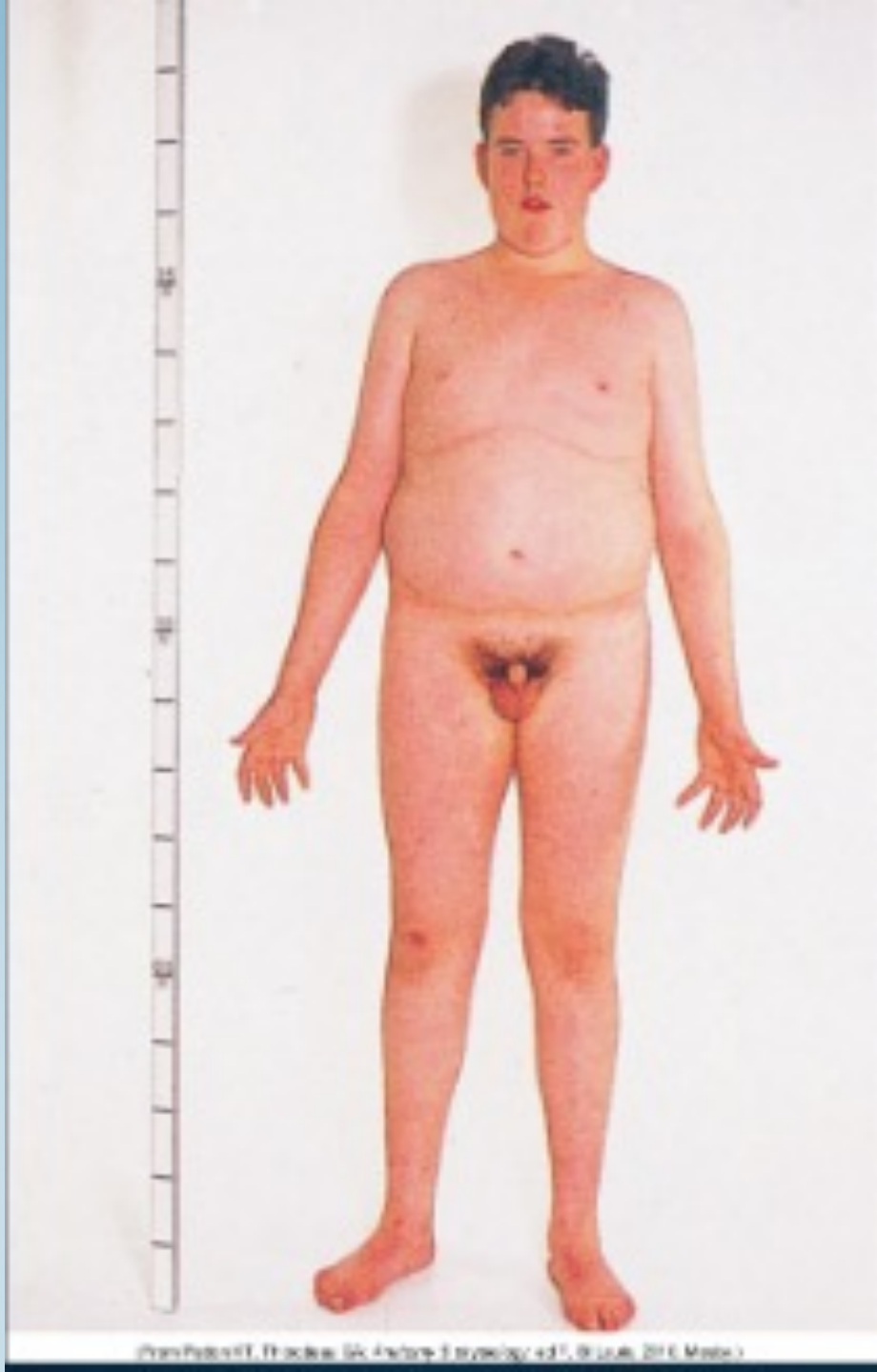
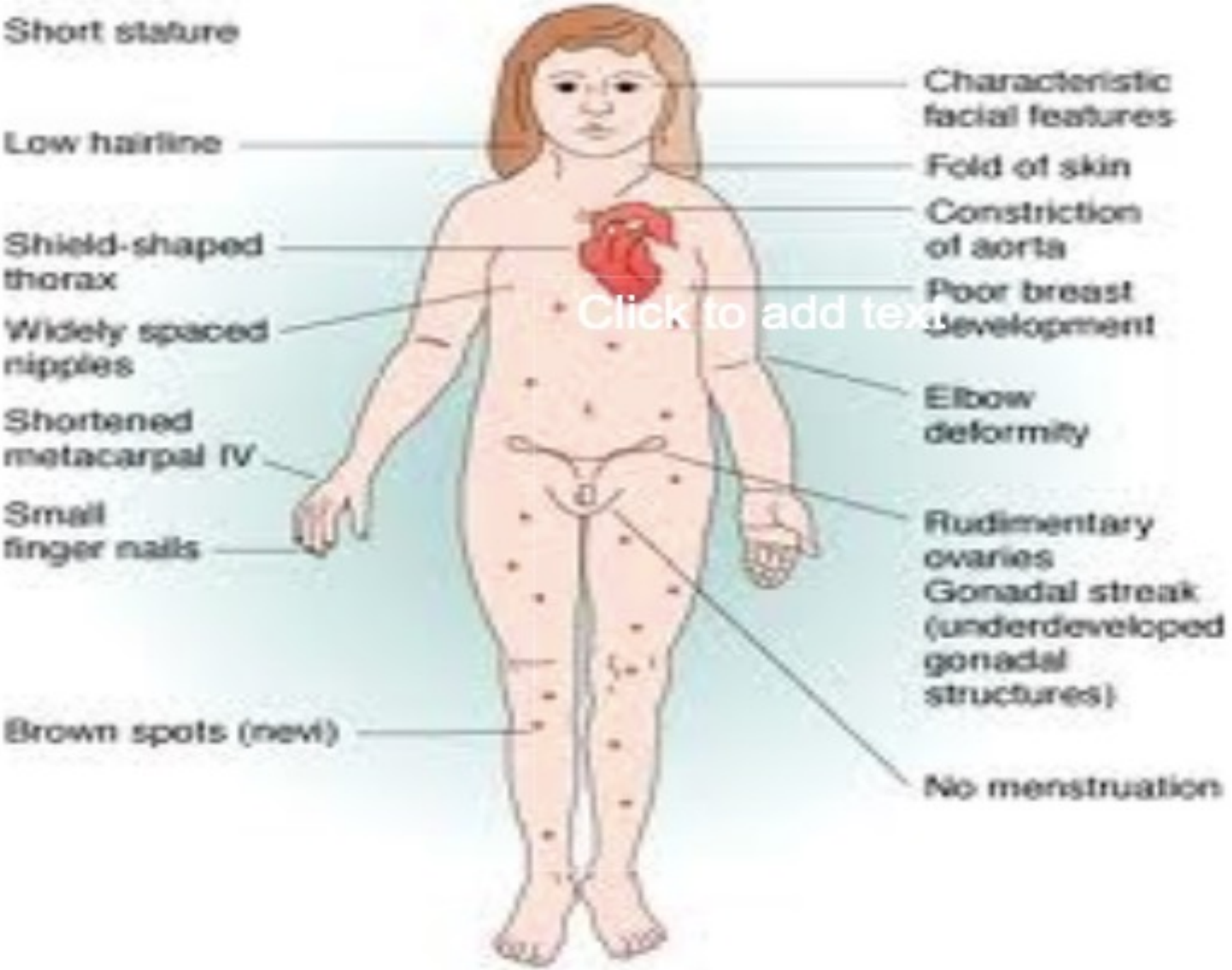


Turner's Syndrome

- Characterized by hypogonadism in females.
- The entire X chromosome is found to be missing in 57% of patients, resulting in a underdeveloped ovaries, short stature.
- Bull neck, and broad chest.
- Individuals are sterile, and lack expected secondary sexual characteristics.
- Mental retardation typically not evident.


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

Turner Syndrome: May Affect Many Body Systems

- Lymphatic
- Cardiac
- Renal
- Ocular
- Auditory
- Skin

- Orthopedic
- Growth
- Ovarian development/ reproduction
- Psychosocial

Marfan's Syndrome

- An inherited disorder that affects connective tissue.
- Marfan syndrome affects the heart, eyes, blood vessels, and bones.
- People with Marfan syndrome are tall and thin with long arms, legs, fingers, and toes.
- Treatment includes medications to keep blood pressure low, eyeglasses or contact lenses, and surgery.

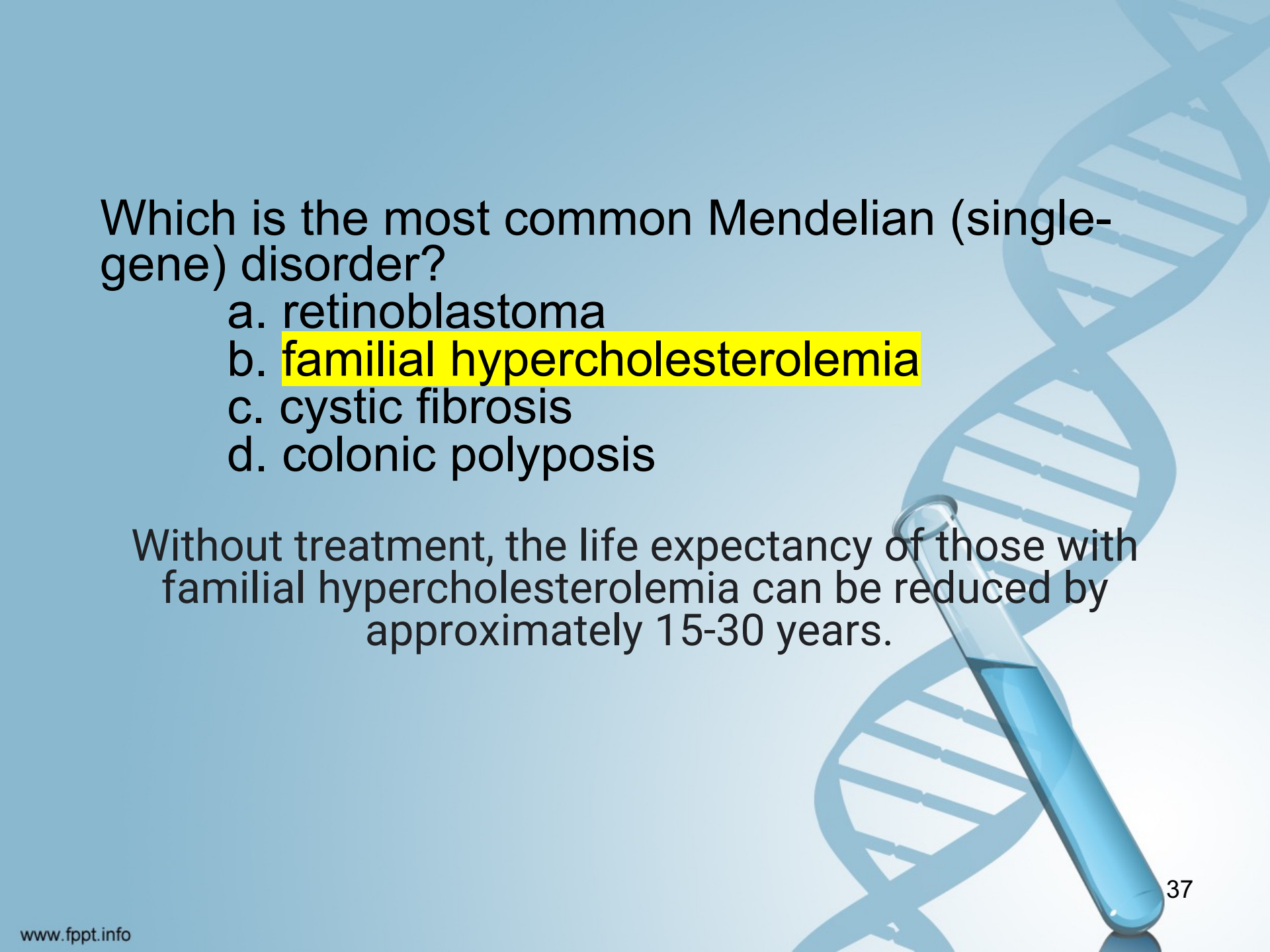
Marfan's disease is a hereditary autosomal dominant syndrome characterized by which of the following?

a. arachnodactyly and joint ankylosis
b. fibrillin-1 gene dysfunction
c. crystalline ectopy and aortic stenosis
d. collagen gene dysfunction

Which is the most common Mendelian (single-gene) disorder?

a. retinoblastoma
b. familial hypercholesterolemia
c. cystic fibrosis
d. colonic polyposis

Without treatment, the life expectancy of those with familial hypercholesterolemia can be reduced by approximately 15-30 years.



Treat Familial Hypercholesterolemia (FH) to Prevent Heart Disease

FH is high risk and not rare

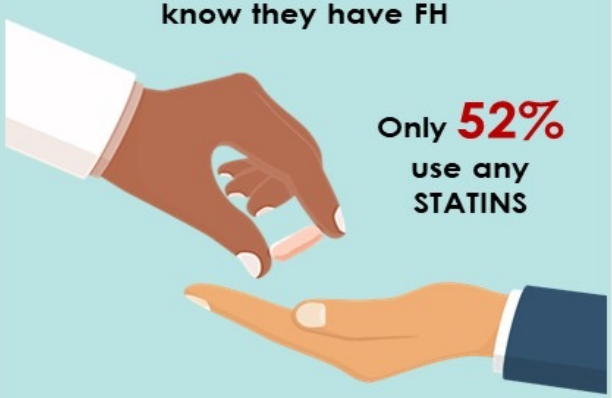
1 in 250
people have FH

and

Up to **22x** increased risk
Of CORONARY HEART DISEASE,
if untreated

Despite known high cholesterol, many undiagnosed, undertreated

More than **80%** know they have HIGH CHOLESTEROL, but most don't know they have FH



Only **52%** use any STATINS

Only **16%** use HIGH INTENSITY STATINS

If you have FH

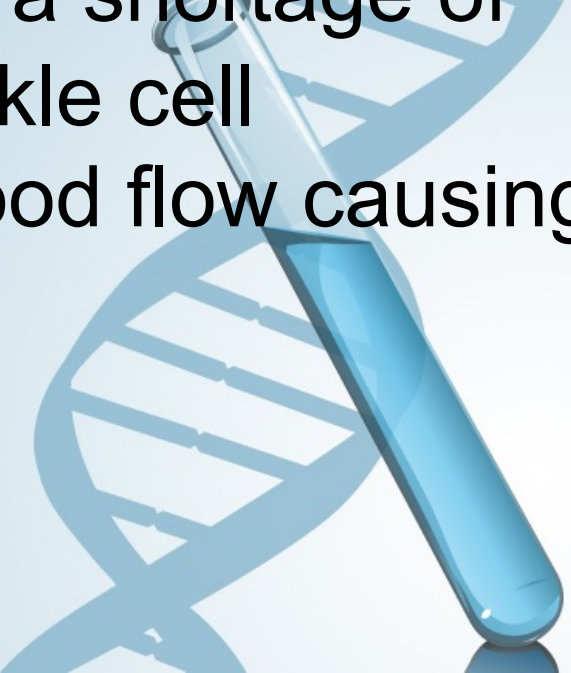
- ASK your doctor about cholesterol-lowering medicines
- TAKE YOUR MEDICINE as directed
- Know that HEALTHY LIFESTYLE is important but often NOT ENOUGH
- CHECK your cholesterol regularly
- TALK to your FAMILY about getting tested for FH

Data from National Health and Nutrition Examination Study: 1999-2014
Bucholz et al. *Circulation* 2018

CDC

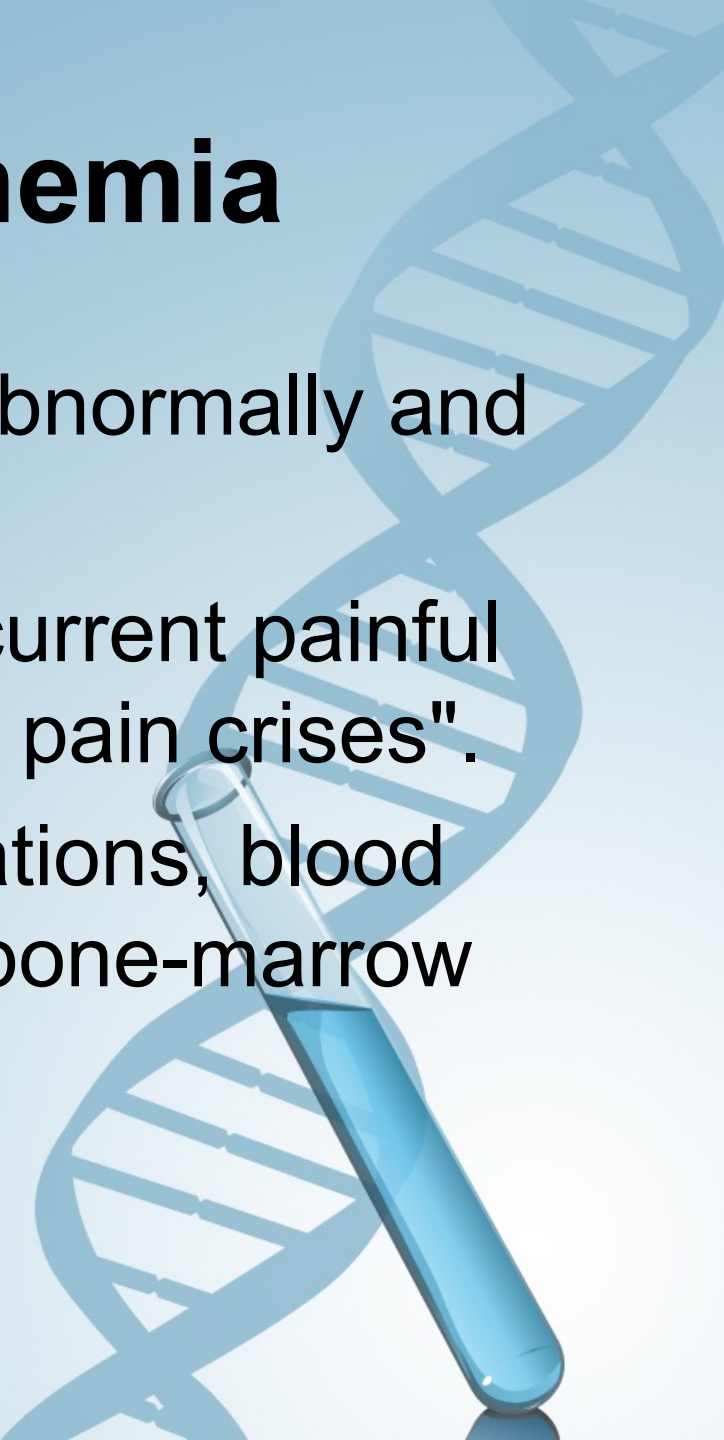
Sickle Cell Anemia

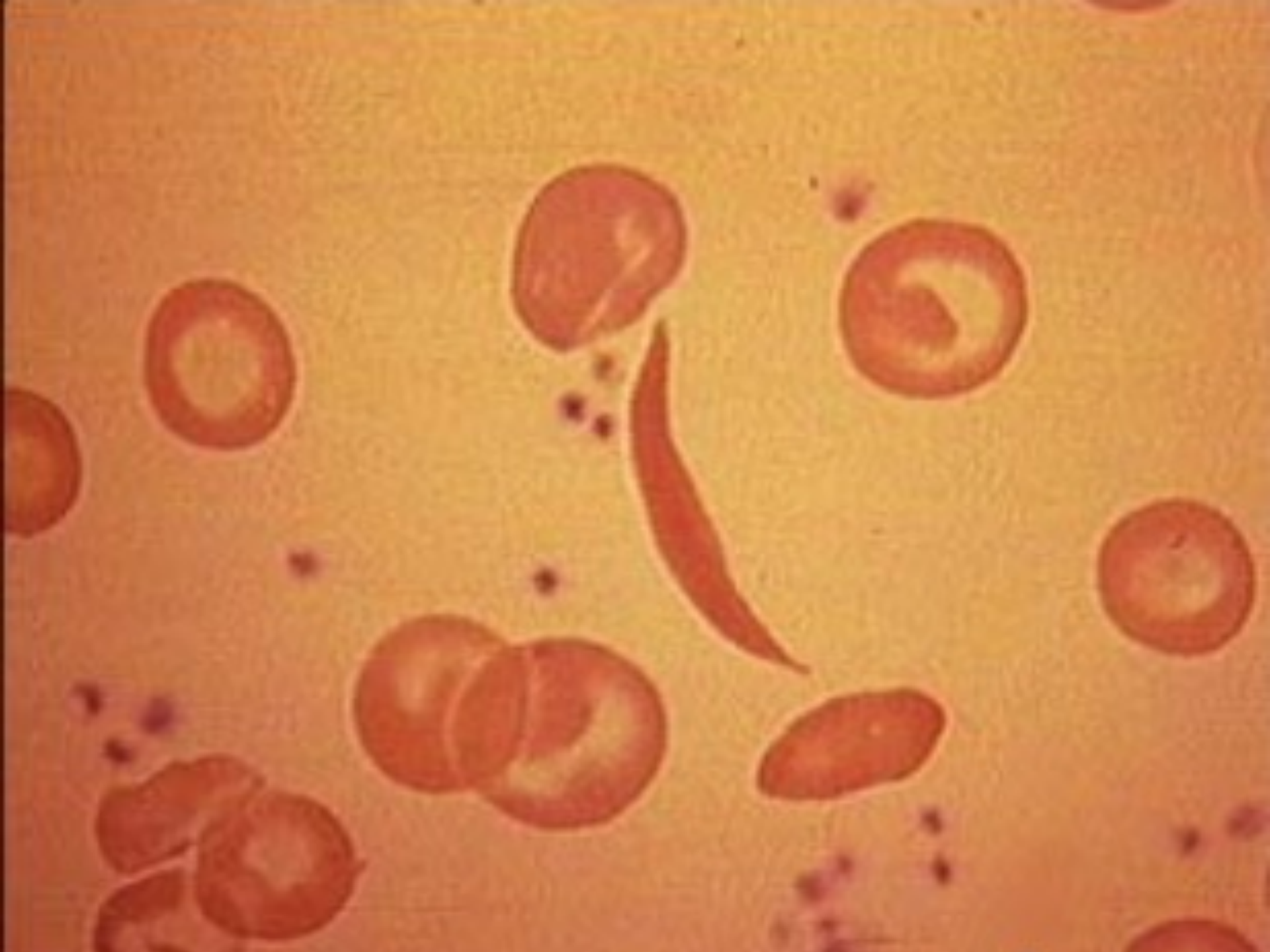
- An inherited, chronic disease in which the red blood cells, normally disc-shaped, become crescent shaped. into a sickle shape.
- The cells die early, leaving a shortage of healthy red blood cells (sickle cell anemia), and can block blood flow causing pain (sickle cell crisis).



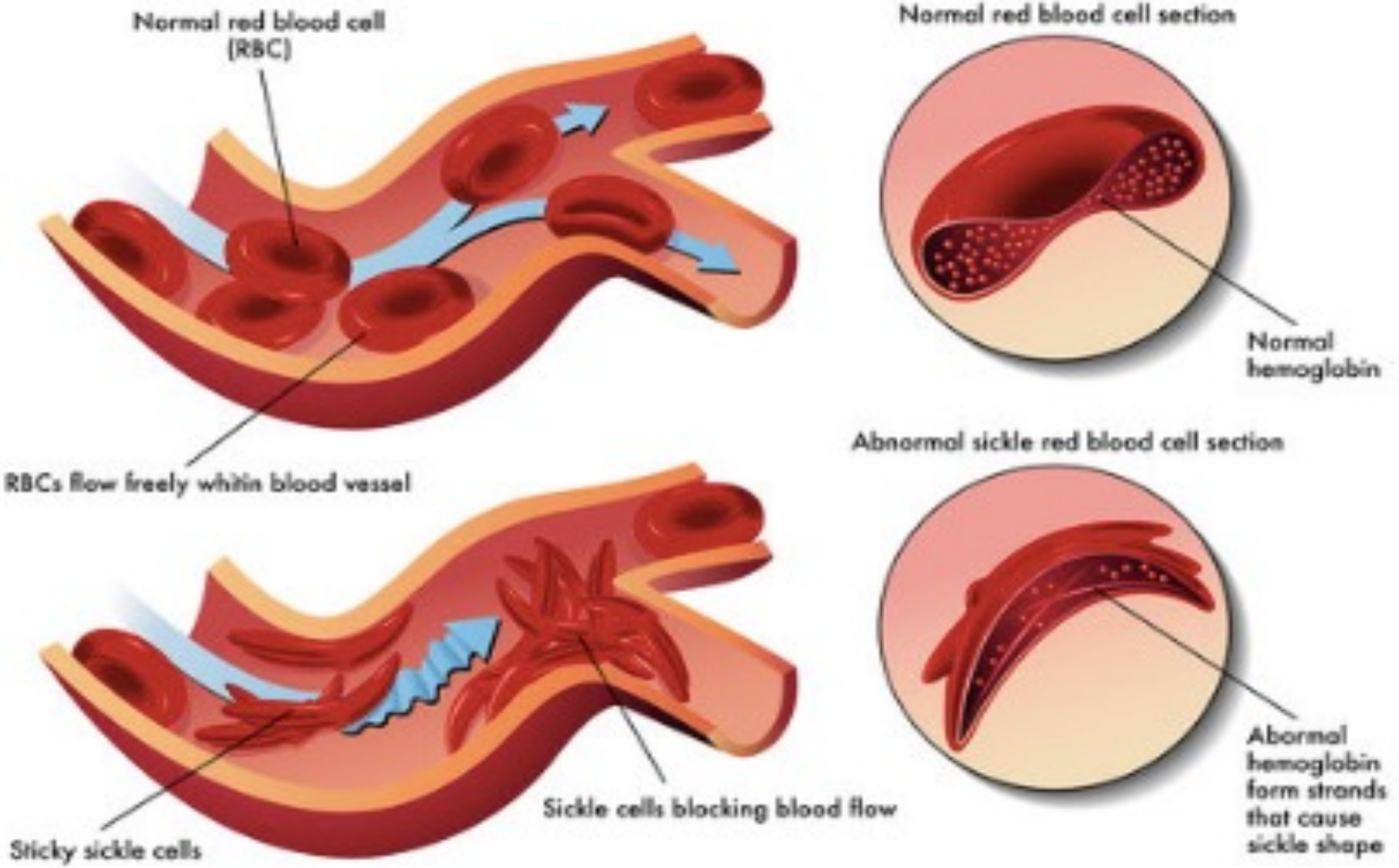
Sickle Cell Anemia

- As a result, they function abnormally and cause small blood clots.
- These clots give rise to recurrent painful episodes called "sickle cell pain crises".
- Treatments include medications, blood transfusions, and rarely a bone-marrow transplant.





Sickle-Cell Anemia



Cystic Fibrosis

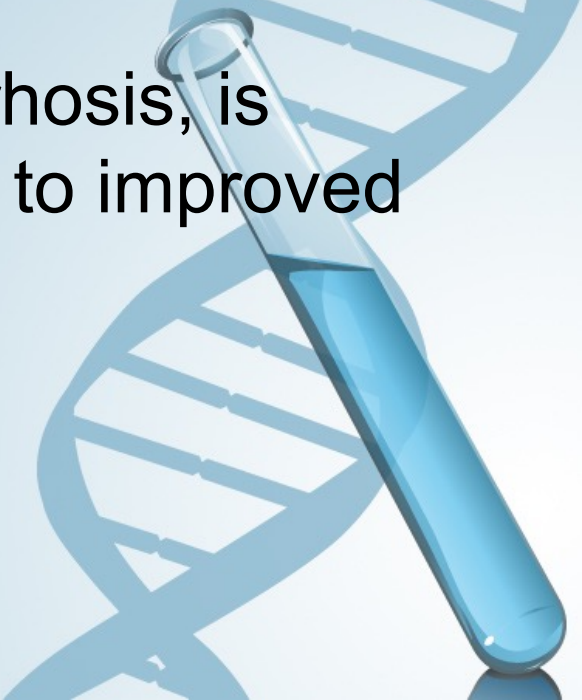
- Inherited disease that causes thick, sticky mucus to build up in the lungs and digestive tract
- The most common type of chronic lung disease in children and young adults
  - 1 in every 3,300 – most children and teenagers
- Cardiopulmonary complications constitute the most common cause of death

Cystic Fibrosis Diagnosis

- Diagnosis
  - Established by the sweat electrolyte test
  - The principal defect is of chloride ion transport, resulting in high salt concentrations in sweat and in viscous luminal secretions in respiratory and gastrointestinal tracts.

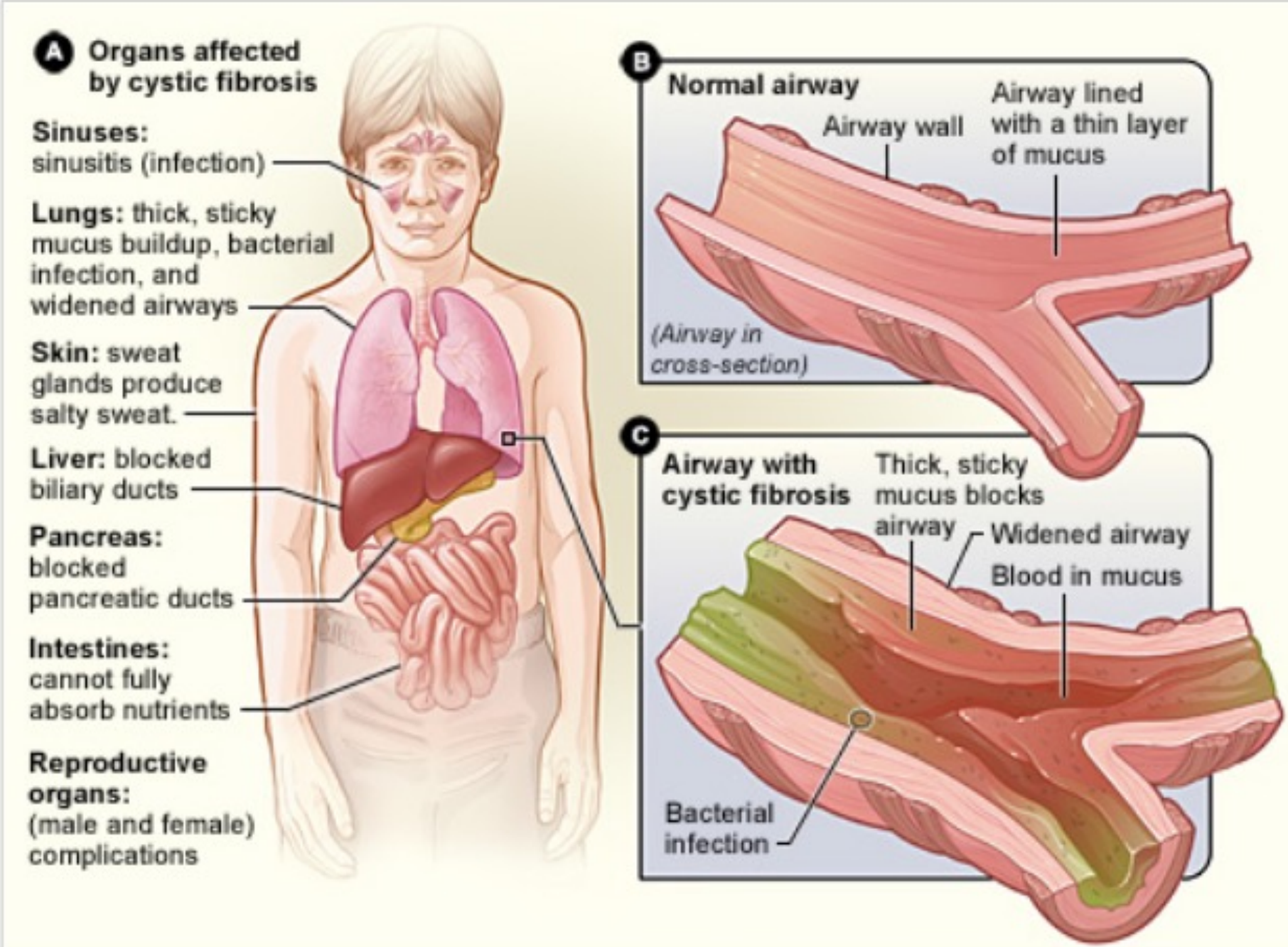
Cystic Fibrosis Symptoms

- Bronchiectasis and right-sided heart failure are long-term sequelae
- Gastrointestinal abnormalities of meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
- Liver disease, including cirrhosis, is increasing in frequency due to improved survival.



Cystic Fibrosis Symptoms

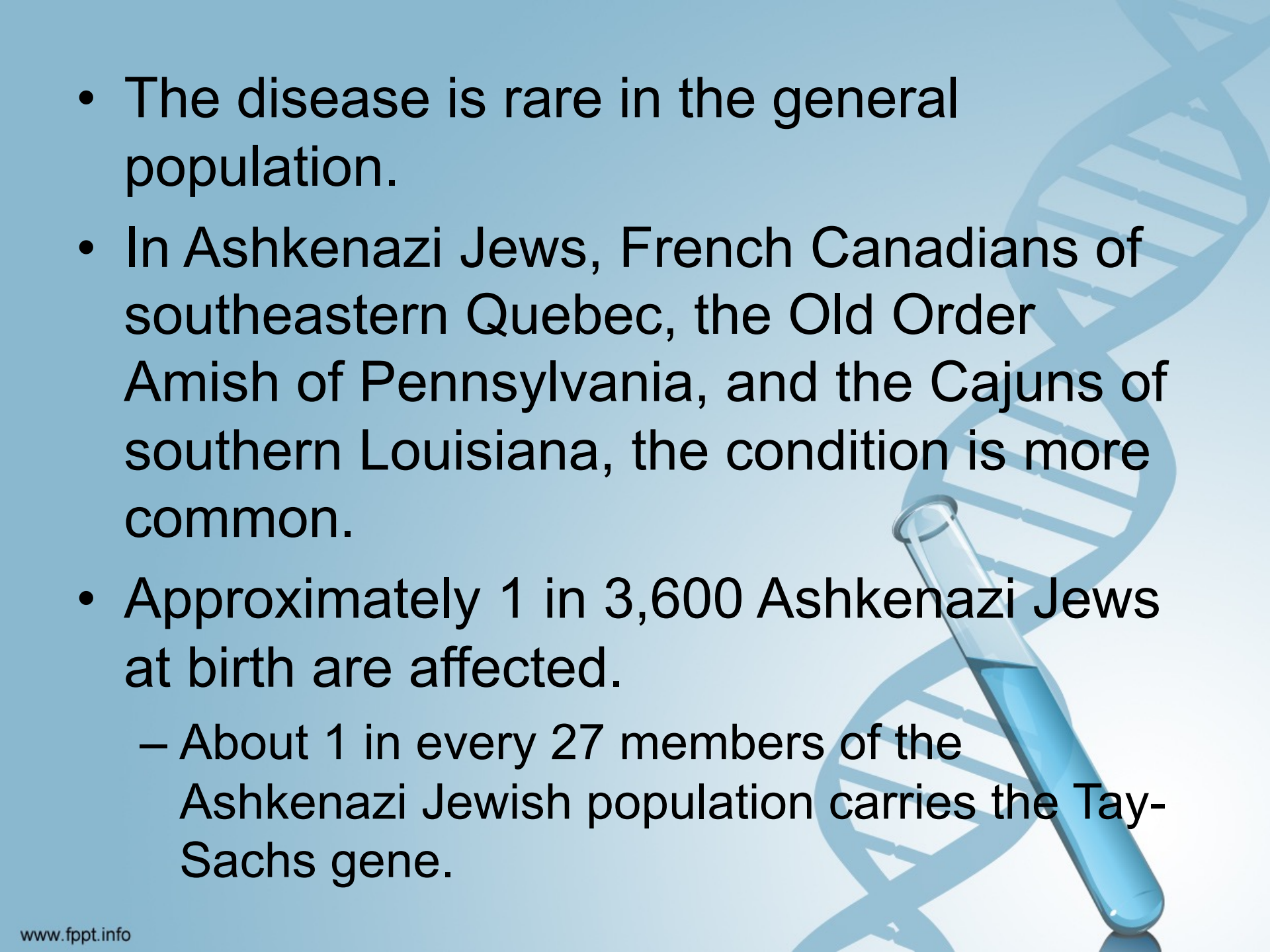
- Pneumonitis, bronchiectasis, lung abscesses, pancreatic insufficiency
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Airway obstruction manifested by wheezing and air trapping
- Bronchiectasis and right-sided heart failure are long-term sequelae
- Gastrointestinal abnormalities of meconium ileus, distal intestinal obstruction syndrome,


A Organs affected by cystic fibrosis
Sinuses: sinusitis (infection)
Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways
Skin: sweat glands produce salty sweat.
Liver: blocked biliary ducts
Pancreas: blocked pancreatic ducts
Intestines: cannot fully absorb nutrients
Reproductive organs: (male and female) complications
B Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C Airway with cystic fibrosis
Thick, sticky mucus blocks airway
Widened airway
Blood in mucus
Bacterial infection

Tay-Sachs Disease

- Tay-Sachs disease is a rare disorder passed from parents to child.
- In the most common form, a baby about 6 months old will begin to show symptoms.
- As the disease progresses, the child's body loses function, leading to blindness, deafness, paralysis and death usually before 2-3 years old.
- That happens because a fatty substance in the child's brain builds up to toxic levels and affects the child's nerve cells.
- There is no cure for Tay-Sachs Disease.

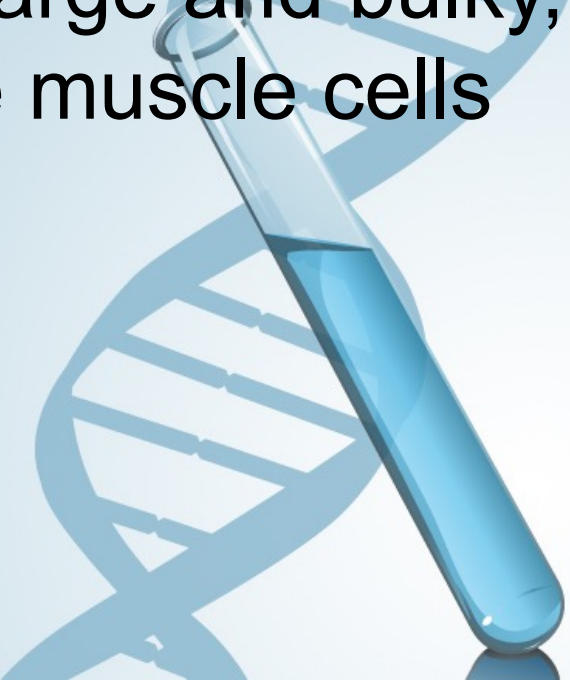
- The disease is rare in the general population.
- In Ashkenazi Jews, French Canadians of southeastern Quebec, the Old Order Amish of Pennsylvania, and the Cajuns of southern Louisiana, the condition is more common.
- Approximately 1 in 3,600 Ashkenazi Jews at birth are affected.
  - About 1 in every 27 members of the Ashkenazi Jewish population carries the Tay-Sachs gene.

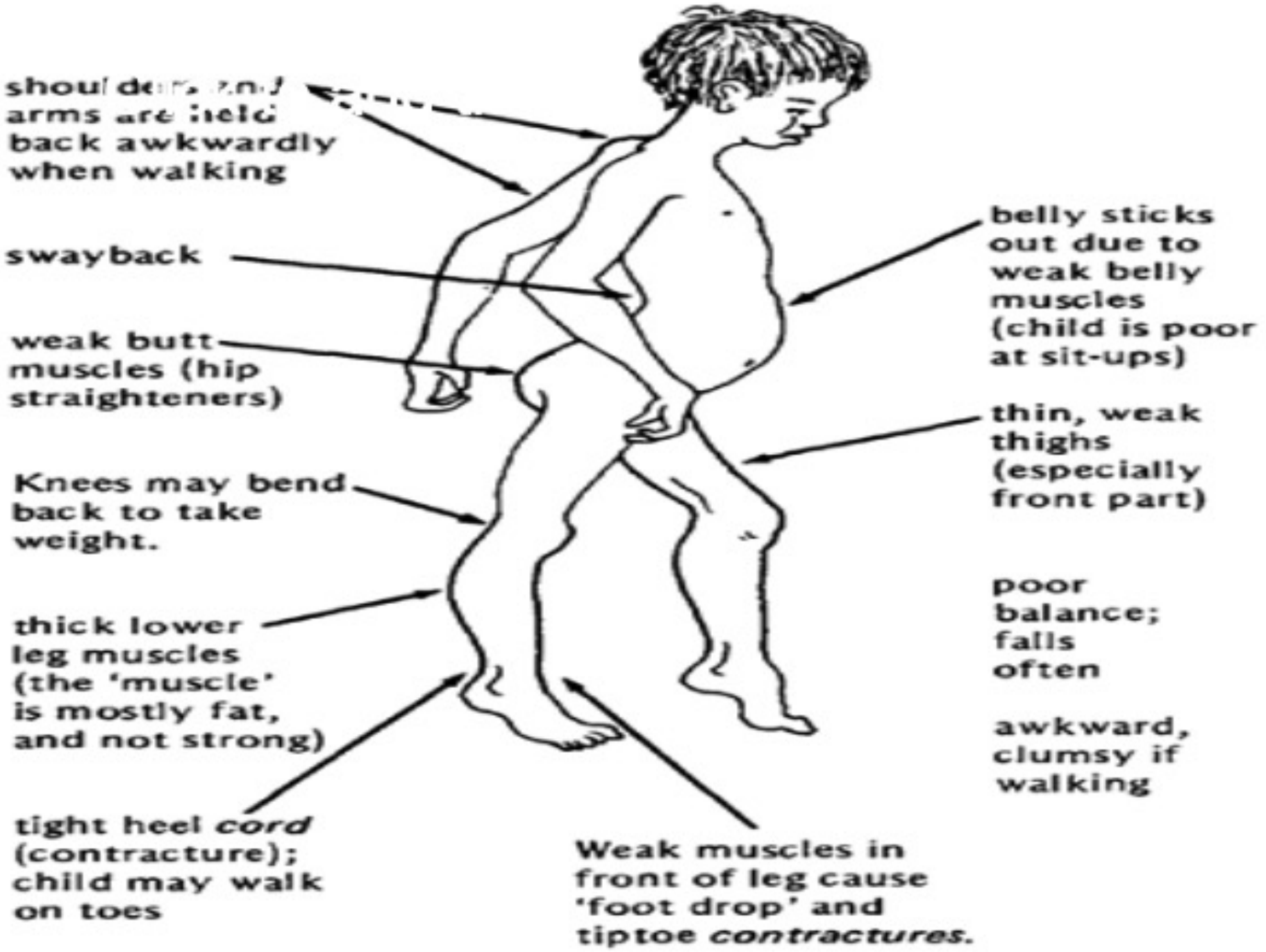


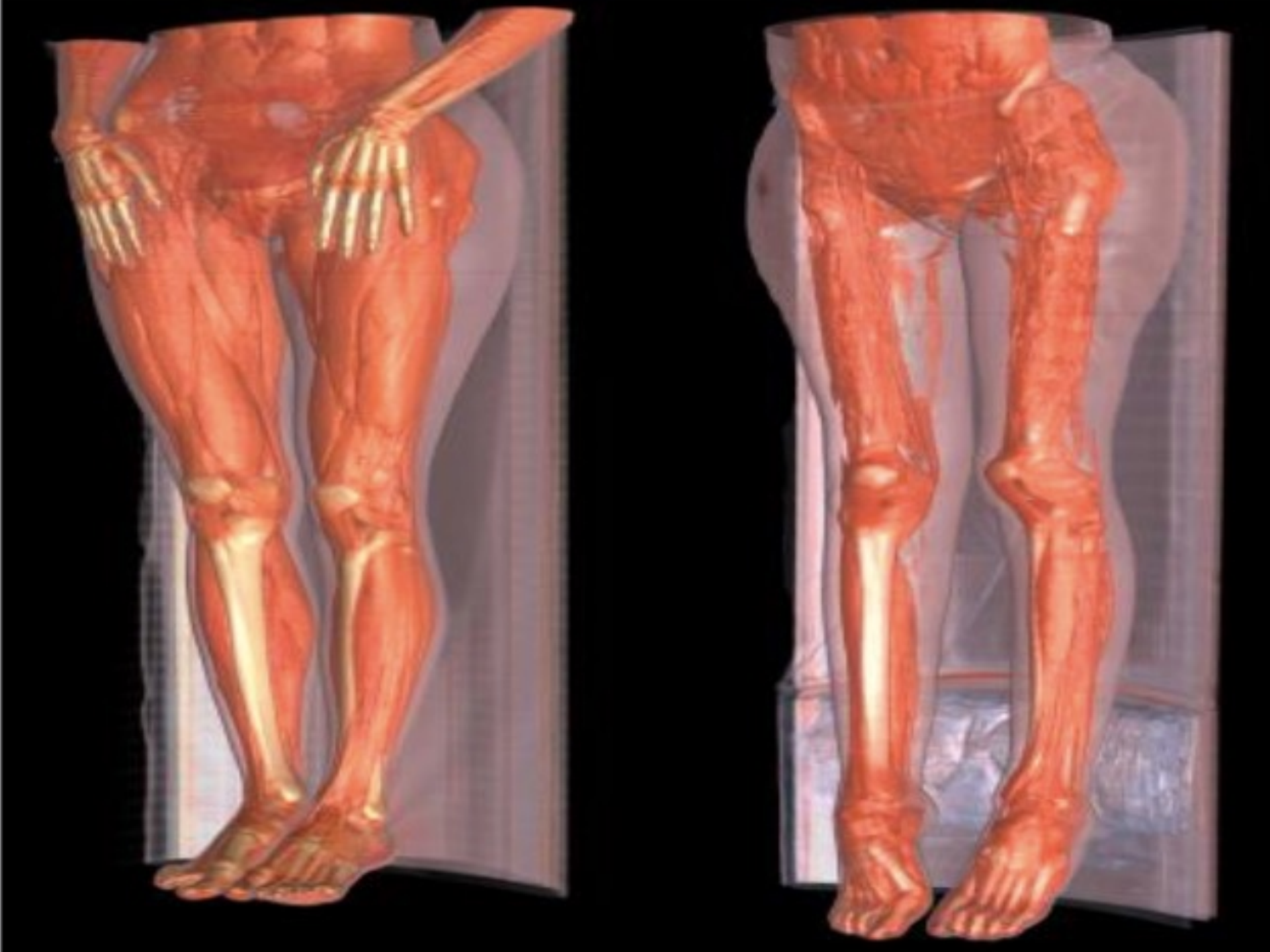
Muscular Dystrophy

- Muscular dystrophy is a disease in which the muscles of the body get weaker and weaker and slowly stop working because of a lack of a certain protein
- Can be passed on by one or both parents, depending on the form of Muscular Dystrophy
  - Females will typically be carriers with males affected. Sons of carrier mothers have a 50% chance of inheriting the defective gene
  - Daughters of mother carriers have a 50% chance of being carriers

- Causes proximal muscle weakness
- Usually affects young boys with weakness of pelvic and shoulder muscles
- The affected muscles are large and bulky, but very weak because the muscle cells do not contract properly




shoulders and arms are held back awkwardly when walking
swayback
weak butt muscles (hip straighteners)
Knees may bend back to take weight.
thick lower leg muscles (the 'muscle' is mostly fat, and not strong)
tight heel *cord* (contracture); child may walk on toes
Weak muscles in front of leg cause 'foot drop' and tiptoe *contractures*.
belly sticks out due to weak belly muscles (child is poor at sit-ups)
thin, weak thighs (especially front part)
poor balance; falls often
awkward, clumsy if walking

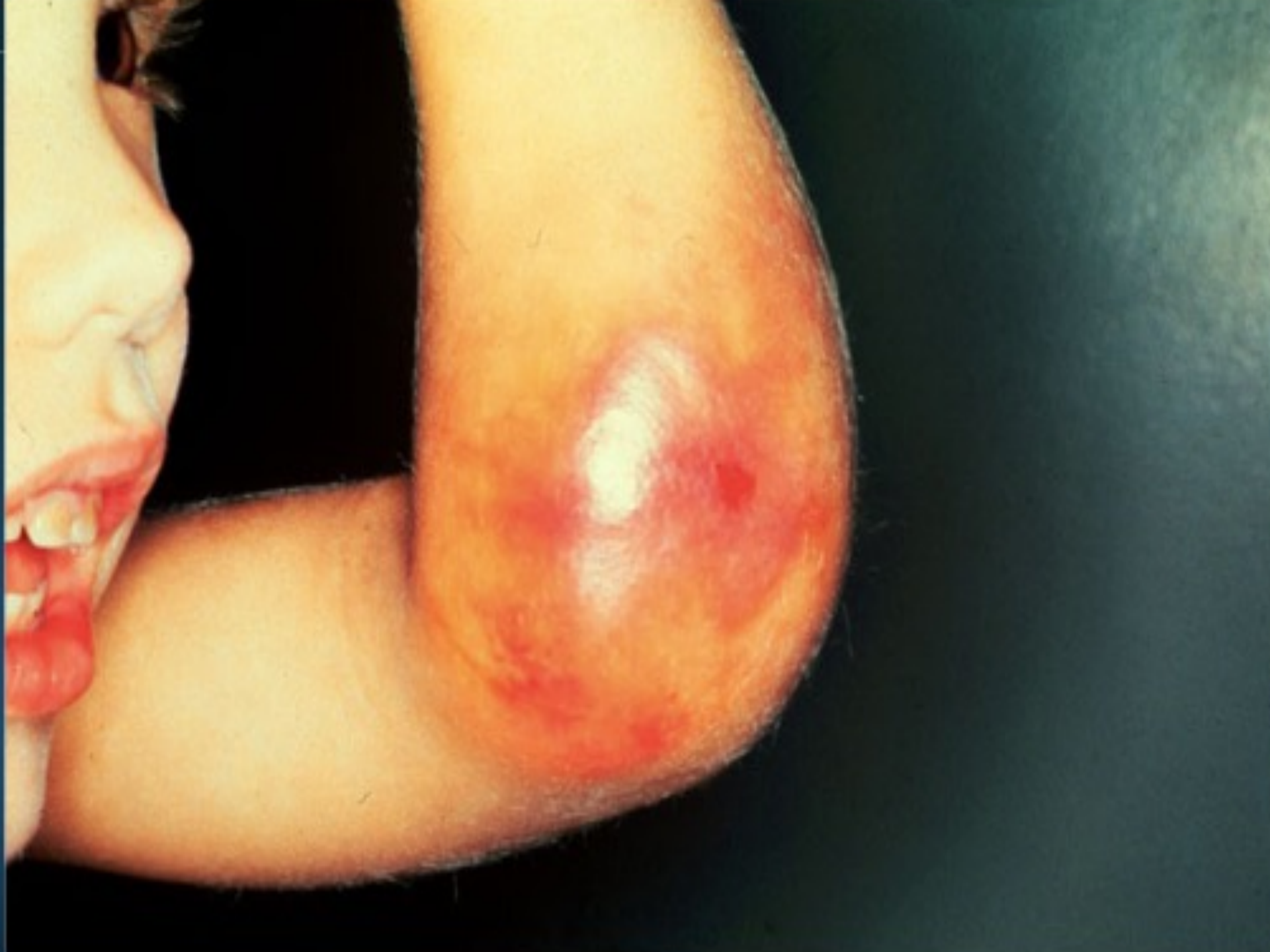


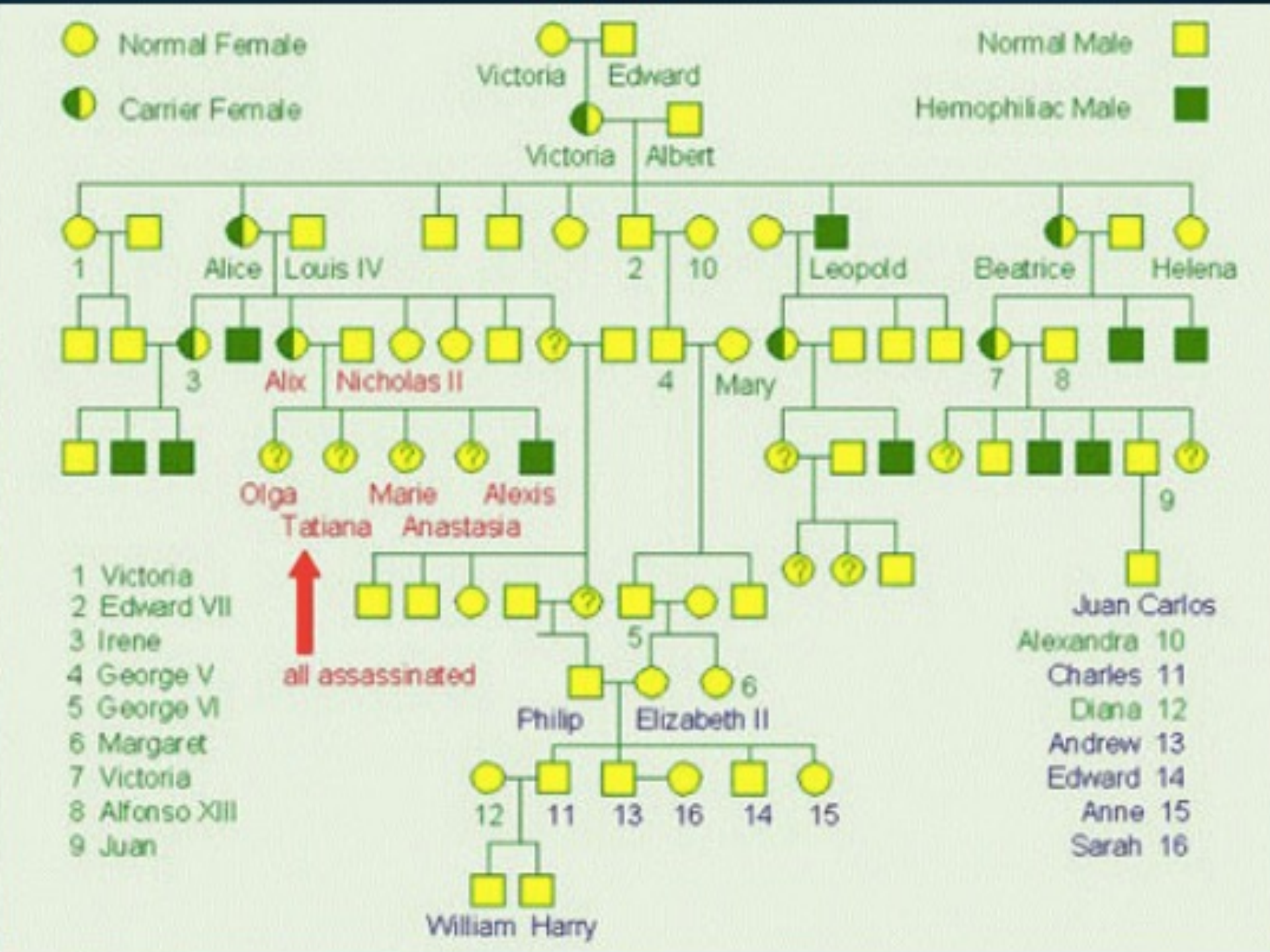
Hemophilia

- Hemophilia is the oldest known hereditary bleeding disorder.
  - The New Testament of the Bible mentioned a woman who had hemorrhaged for 12 years, before touching the hem of Jesus' garment, when she was healed.
  - Hemophilia is sometimes referred to as "the royal disease" because it affected the royal families of England, Germany, Russia and Spain in the 19th and 20th centuries. Queen Victoria of England is believed to have been the carrier of hemophilia B, or factor IX deficiency. She passed the trait on to three of her nine children.

- A medical condition in which the ability of the blood to clot is severely reduced, causing the sufferer to bleed severely from even a slight injury.
- The condition is typically caused by a hereditary lack of a coagulation factor, most often factor VIII.
- There are about 20,000 hemophilia patients in the United States.

- One can bleed to death with small cuts.
- The severity of hemophilia is related to the amount of the clotting factor in the blood. About 70% of hemophilia patients have less than one percent of the normal amount and, thus, have severe hemophilia.




Normal Female
Carrier Female
Normal Male
Hemophiliac Male
Victoria
Edward
Victoria
Albert
1
Alice
Louis IV
2
10
Leopold
Beatrice
Helena
3
Alix
Nicholas II
4
Mary
7
8
Olga
Tatiana
Marie
Anastasia
Alexis
9
1 Victoria
2 Edward VII
3 Irene
4 George V
5 George VI
6 Margaret
7 Victoria
8 Alfonso XIII
9 Juan
all assassinated
5
6
Philip
Elizabeth II
12
11
13
16
14
15
William
Harry
Juan Carlos
Alexandra 10
Charles 11
Diana 12
Andrew 13
Edward 14
Anne 15
Sarah 16

Huntington’s Disease

- Huntington's disease (HD) is an inherited, degenerative brain disorder which results in an eventual loss of both mental and physical control.
- The disease is also known as Huntington's chorea.
- Chorea means "dance-like movements" and refers to the uncontrolled motions often associated with the disease.

- Most people with Huntington's disease develop signs and symptoms in their 40s or 50s, but the onset of disease may be earlier or later in life.
- When disease onset begins before age 20, the condition is called juvenile Huntington's disease.
- Earlier onset often results in a somewhat different presentation of symptoms and faster disease progression.

Healthy brain

Huntington's disease

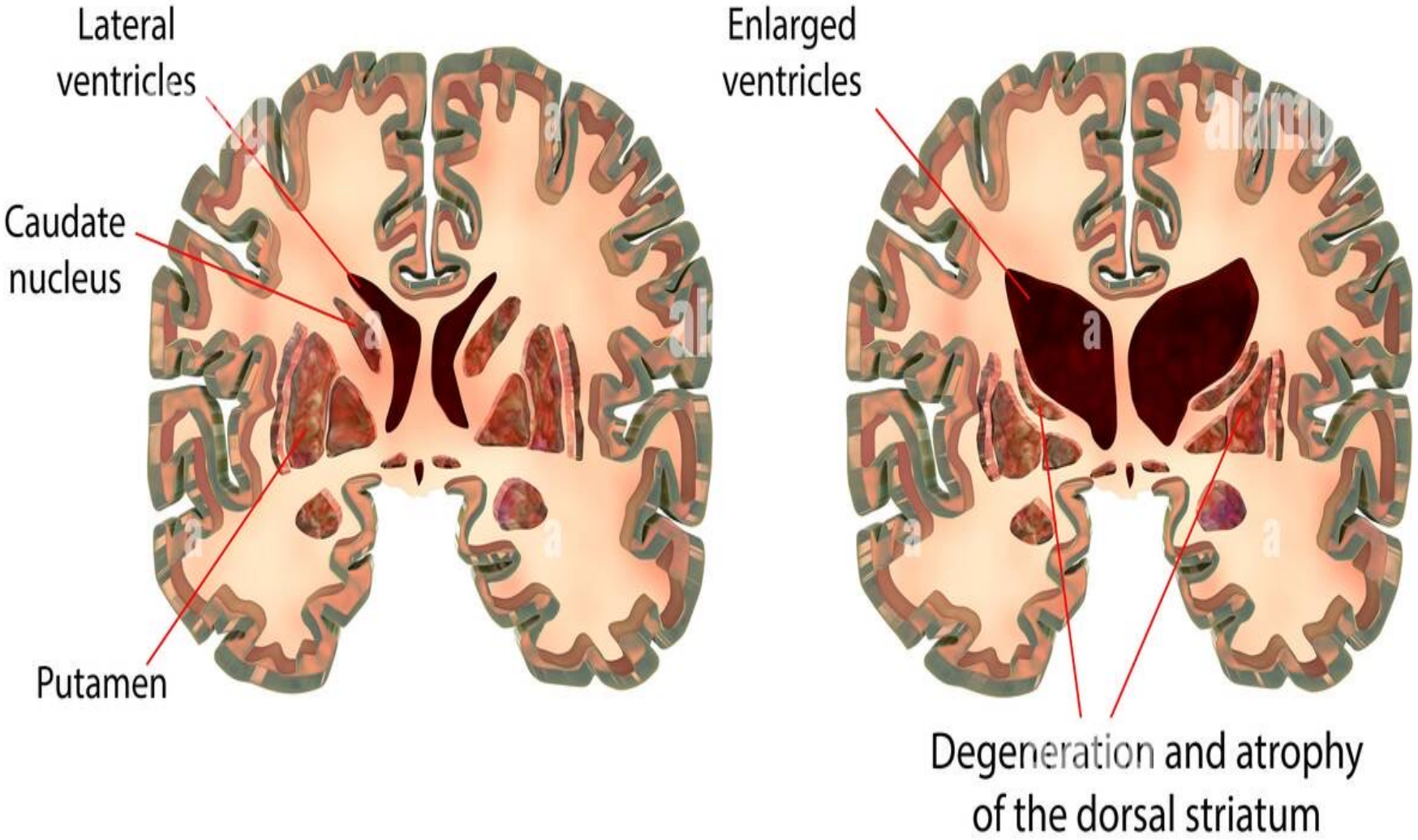
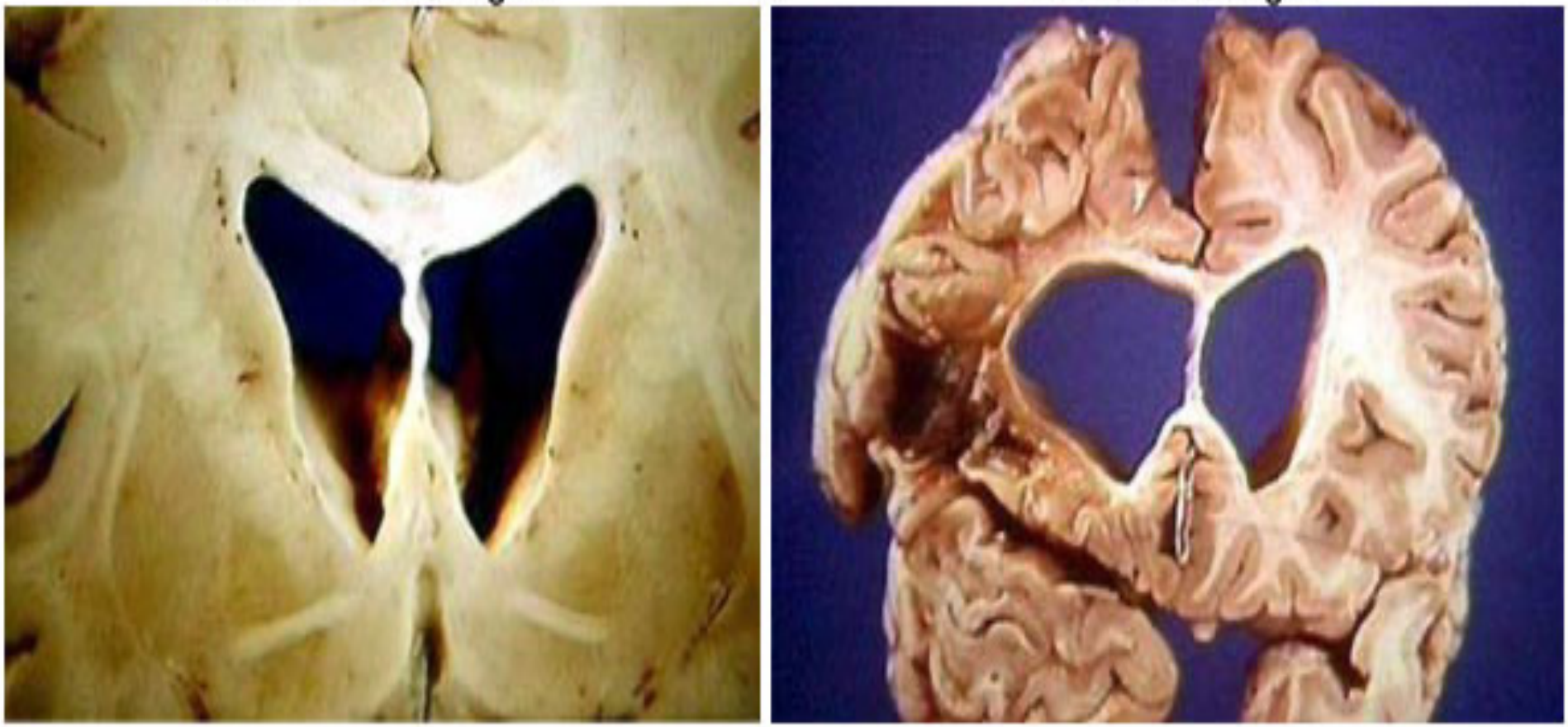


Figure D-4: Effect of HD on the Basal Ganglia

Normal Basal Ganglia vs. HD Basal Ganglia



The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region.

Source: Singer, Jonathan. Huntington's Disease. Online. Available at: http://ist-socrates.berkeley.edu/~jmp/HD.html

Phenylketonuria or PKU

- People with PKU cannot consume any product that contains aspartame.
- PKU is a metabolic disorder that results when the PKU gene is inherited from both parents.
- Caused by a deficiency of an enzyme which is necessary for proper metabolism of an amino acid called phenylalanine.
  - Phenylalanine is an essential amino acid and is found in nearly all foods which contain protein, dairy products, nuts, beans, tofu… etc.

- A low protein diet must be followed.
- Brain damage can result if the diet is not followed causing mental retardation…and mousy or musty body odor (phenylacetic acid is in sweat).
- Phenylalanine-free diet

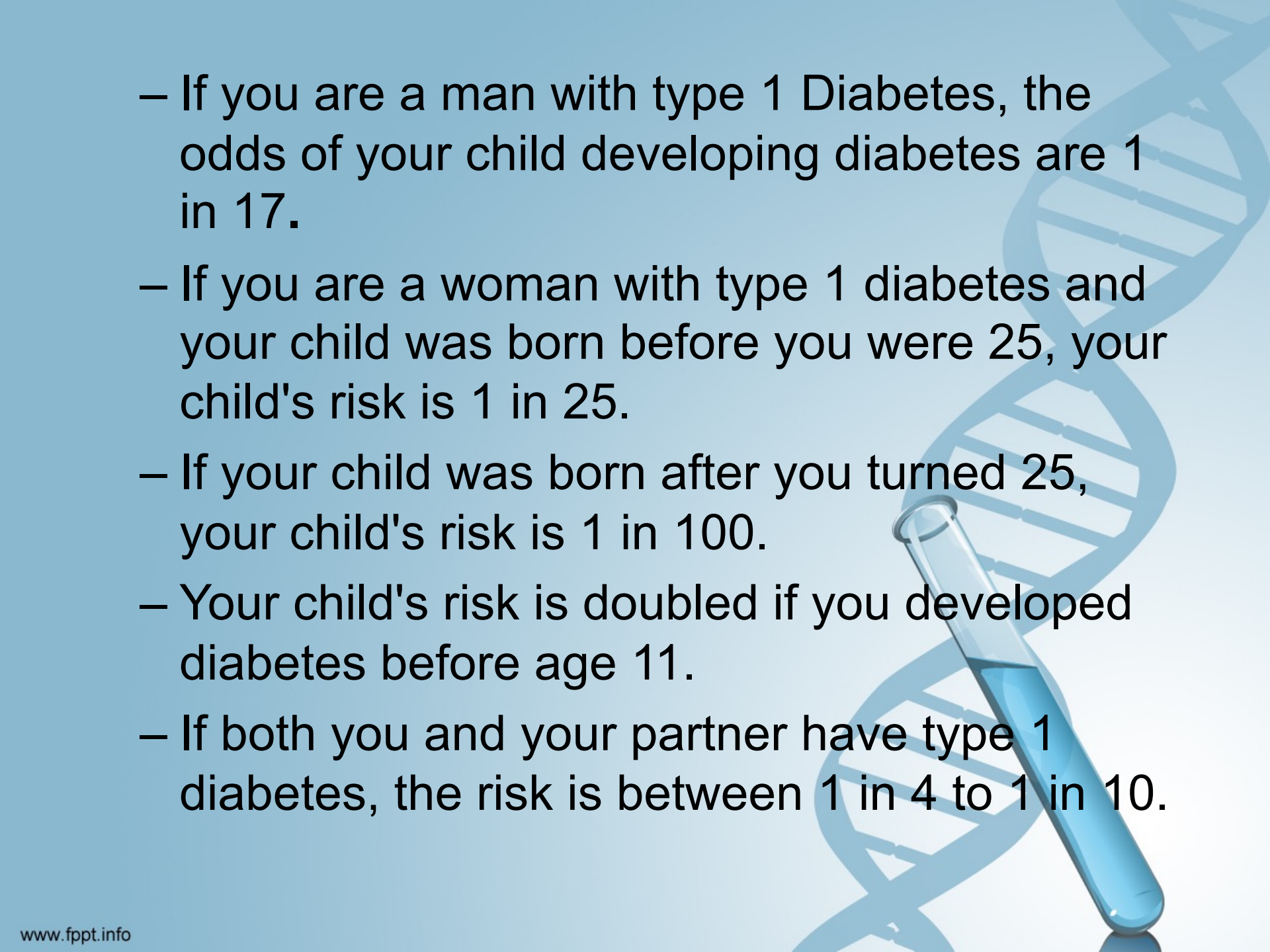
Amyotrophic Lateral Sclerosis

- The disease strikes people between the ages of 40 and 70, and as many as 30,000 Americans have the disease at any given time.
- This mutation is believed to make a defective protein that is toxic to motor nerve cells.
- A common first symptom is a painless weakness in a hand, foot, arm or leg, other early symptoms include speech swallowing or walking difficulty.

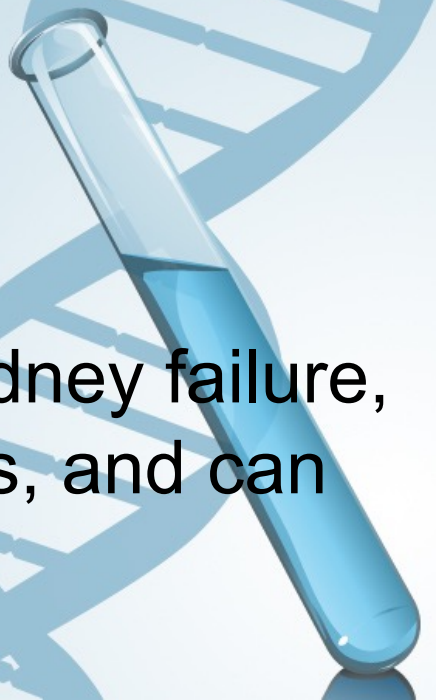
Diabetes

- Disease in which the body does not produce or properly use insulin.
  - Insulin is a hormone that is needed to convert sugar, starches, and other food into energy needed for daily life.
- Genetic mutation can lead to Type 1 Diabetes.

- If you are a man with type 1 Diabetes, the odds of your child developing diabetes are 1 in 17.
- If you are a woman with type 1 diabetes and your child was born before you were 25, your child's risk is 1 in 25.
- If your child was born after you turned 25, your child's risk is 1 in 100.
- Your child's risk is doubled if you developed diabetes before age 11.
- If both you and your partner have type 1 diabetes, the risk is between 1 in 4 to 1 in 10.

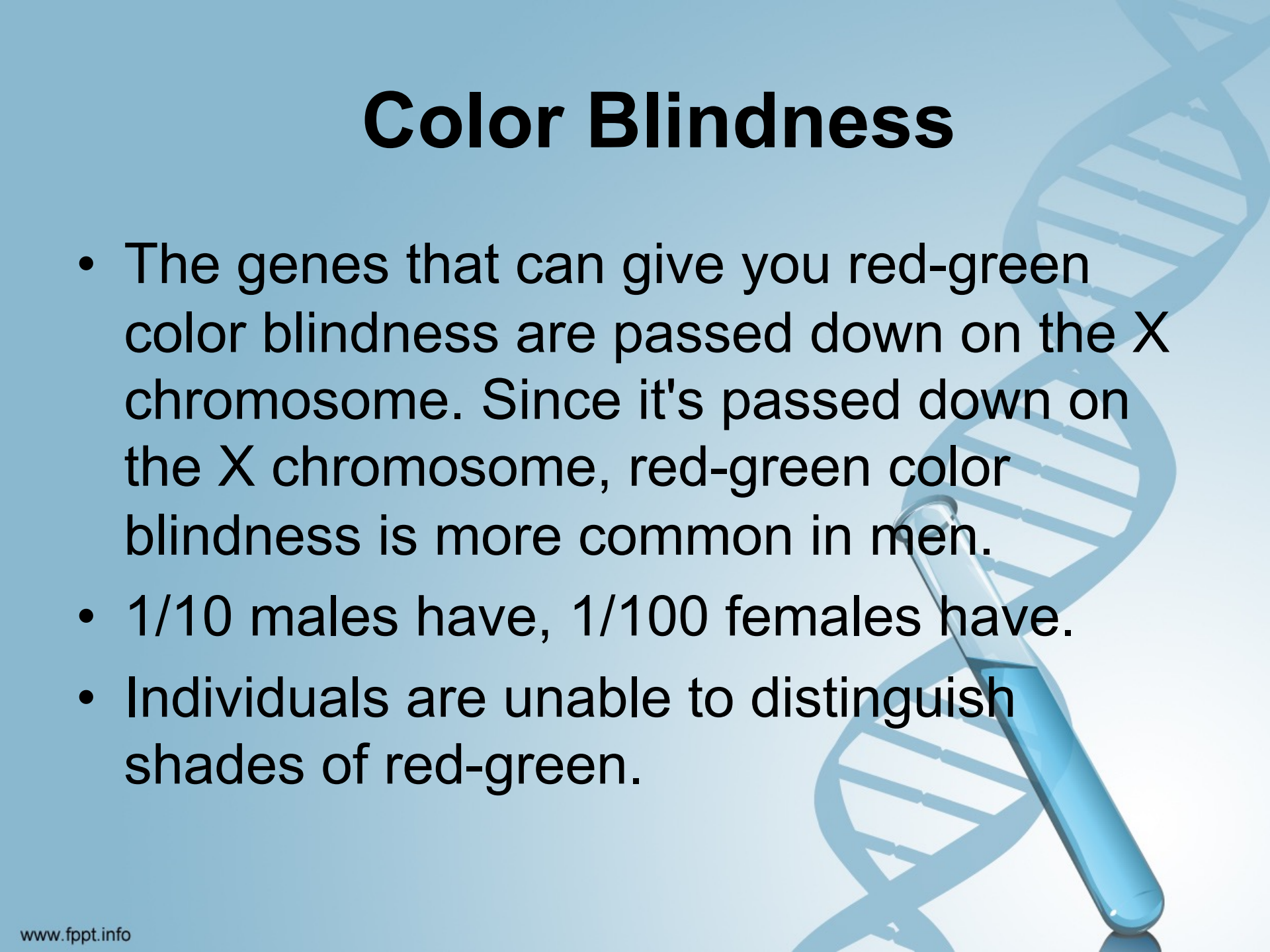


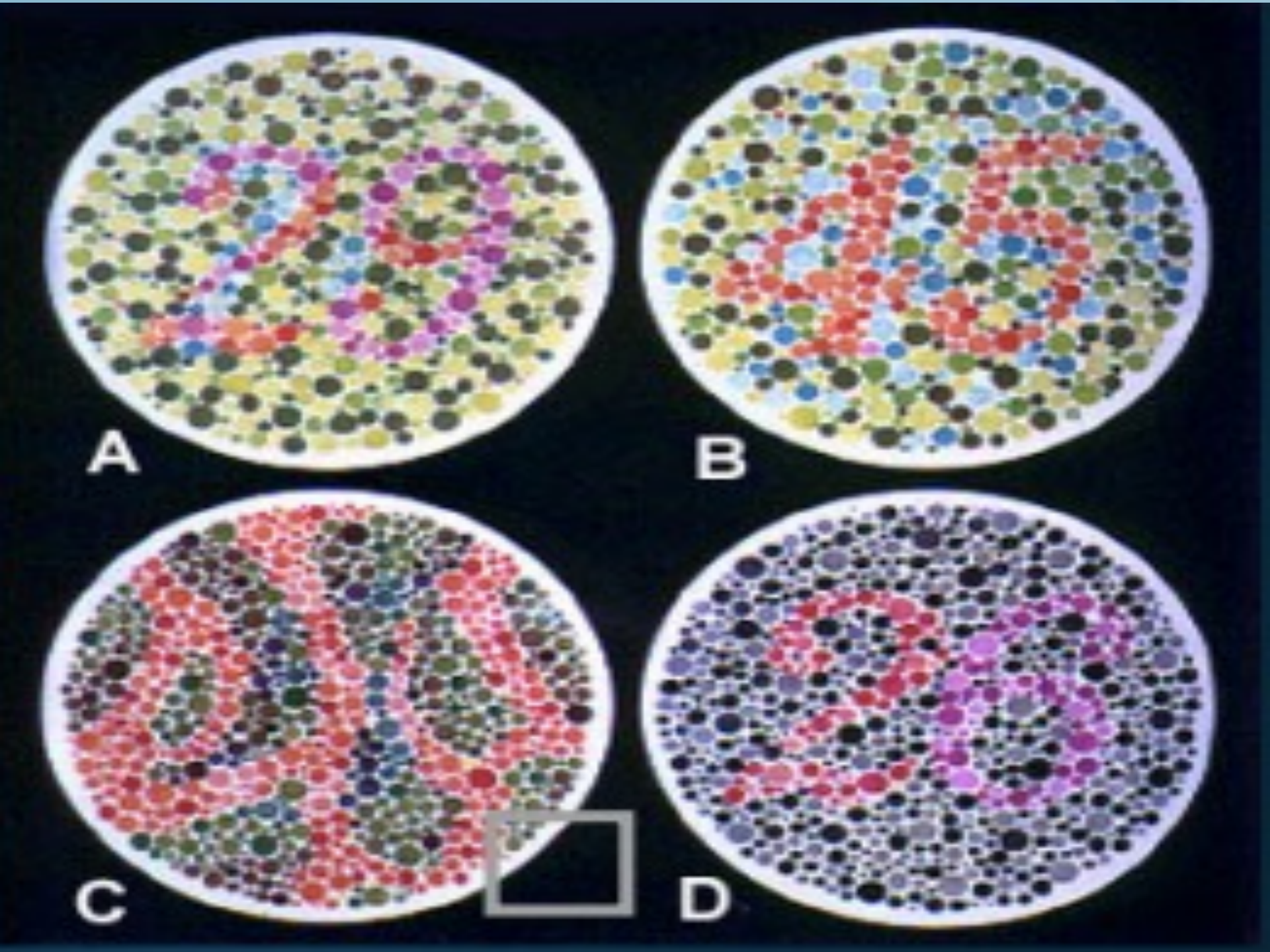
- Type 1 reveals itself in childhood an is referred to as Juvenile Onset Diabetes.
- Type 2 is referred to as adult onset diabetes is related to lifestyle.
- 3 classic symptoms – Polydipsia, Polyuria, Polyphagia
- Warning signs
  - Blurry vision from time to time
  - Unusual fatigue or drowsiness
  - Unexplained weight loss
- Diabetes is the leading cause of kidney failure, blindness, and amputation in adults, and can also lead to heart disease.



Color Blindness

- The genes that can give you red-green color blindness are passed down on the X chromosome. Since it's passed down on the X chromosome, red-green color blindness is more common in men.
- 1/10 males have, 1/100 females have.
- Individuals are unable to distinguish shades of red-green.




A
B
C
D

Albinism

- Patients are unable to produce skin or eye pigments, and are light-sensitive.
- The cause of albinism is a defect in one of several genes that produce or distribute melanin, the pigment that gives skin, eyes, and hair their coloring.
- The defect may result in the absence of melanin production or a reduced amount of melanin production.

Albinism

- The incidence rate in most populations is 1 in 40,000 births.
- The incidence rate in the USA is 1 in 17,000 births. Approximately 1 in 18,000 current cases in the USA.