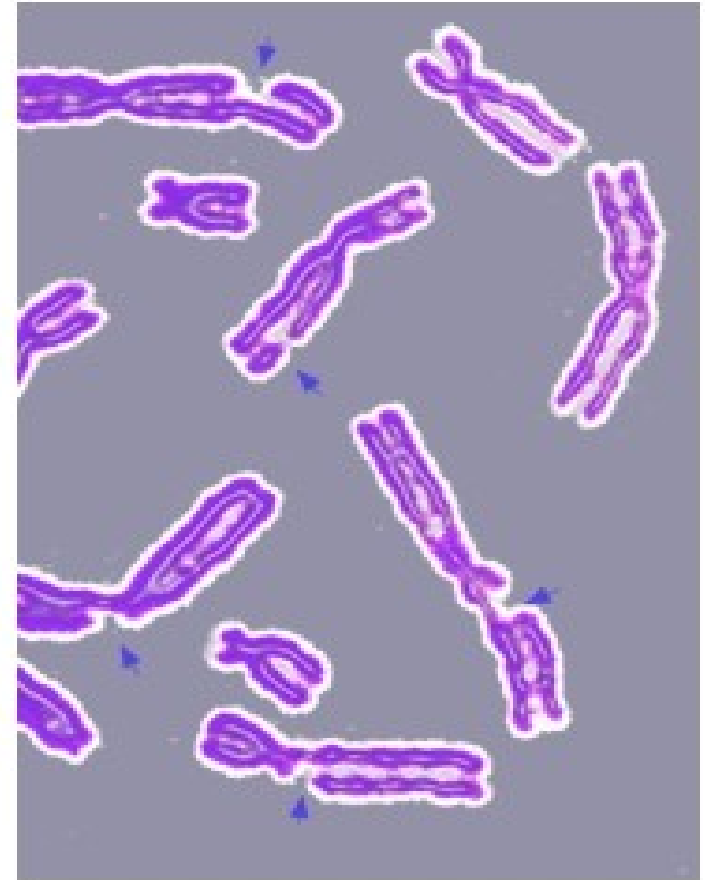


L'origine della variabilità genetica

Ricombinazione e mutazioni

- Le risorse sulle quali opera la selezione naturale sono le variazioni genetiche esistenti in una popolazione di individui.
- Queste variazioni si originano essenzialmente grazie a due processi fondamentali: le **mutazioni** e la **ricombinazione genica**.
- Con il procedere dell'evoluzione, la ricombinazione tra i genotipi esistenti da origine ad una nuova gamma di variazioni.
- Bisogna tener conto che **le variazioni introdotte** da eventi di mutazione e ricombinazione genica **sono assolutamente casuali** rispetto alla direzione dell'adattamento evolutivo.



Un esempio di mutazioni cromosomiche. Le frecce indicano zone di frattura del DNA.

Padre

Madre

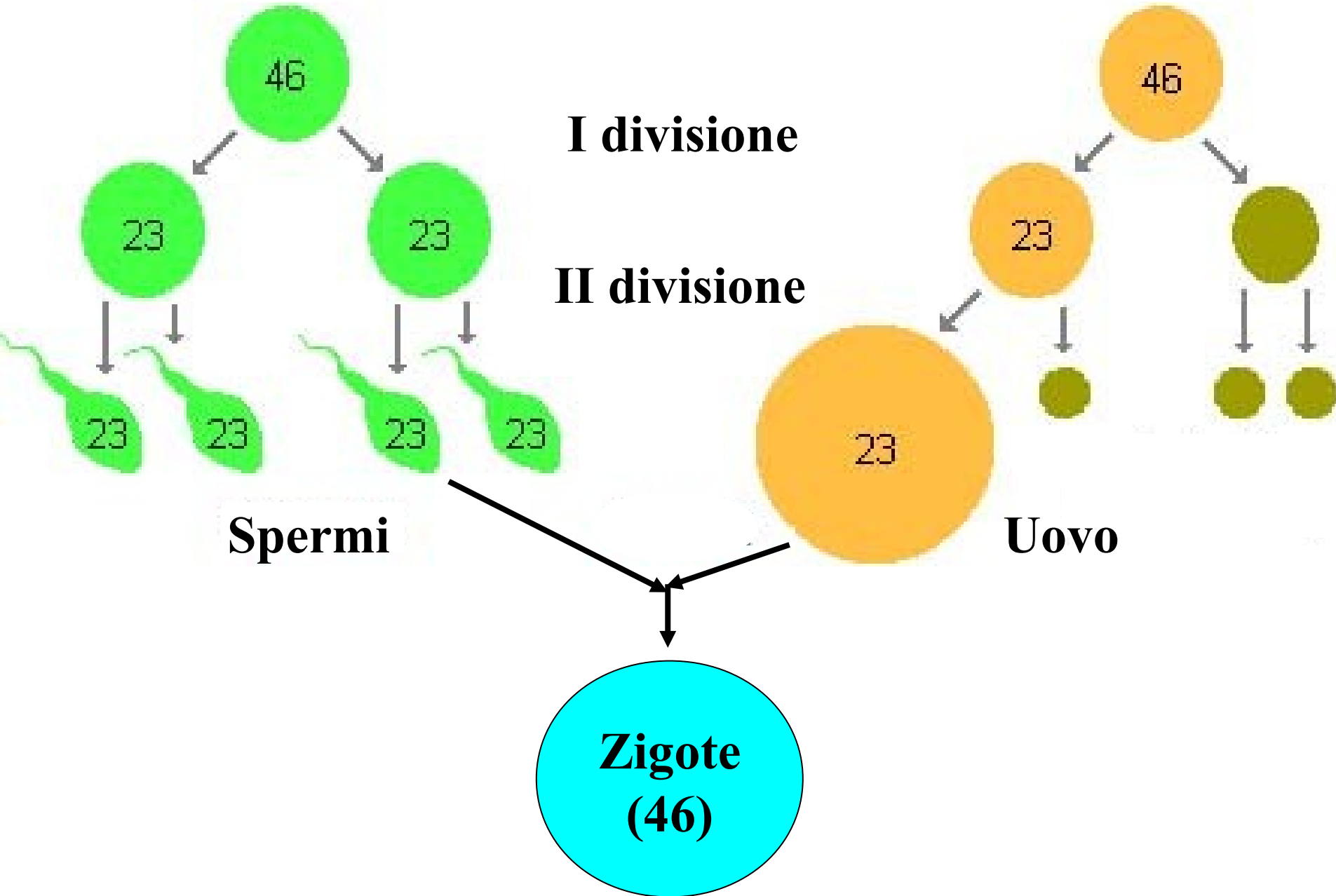
I divisione

II divisione

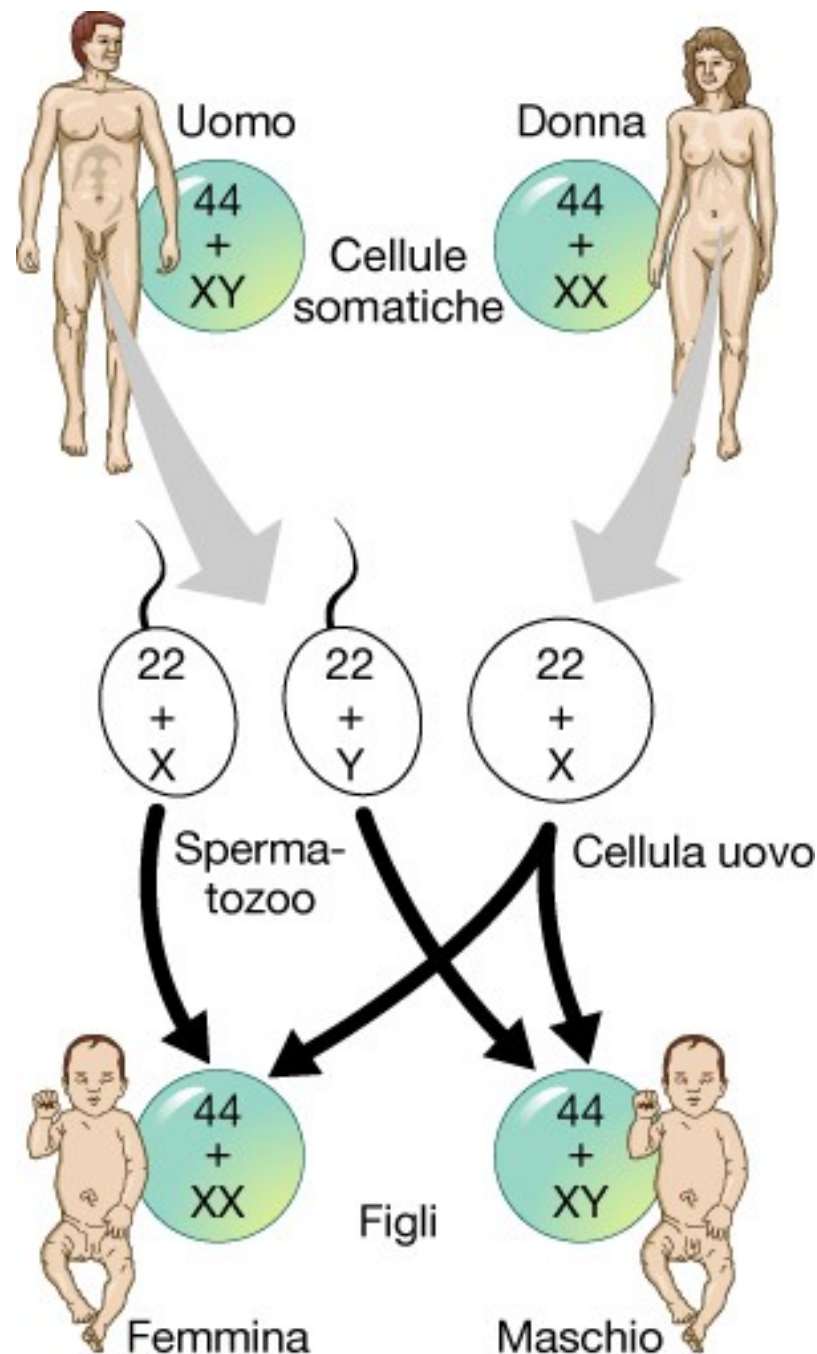
Spermi

Uovo

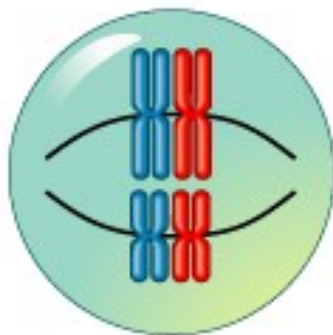
**Zigote
(46)**



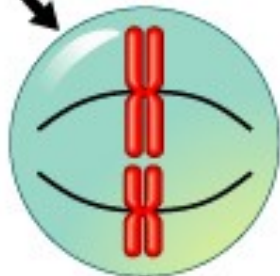
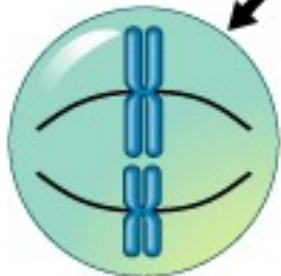
La determinazione del sesso nell'uomo dipende dall'assortimento dei cromosomi "X" e "Y"



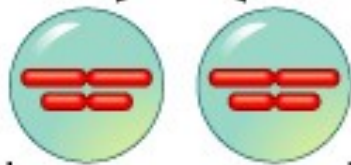
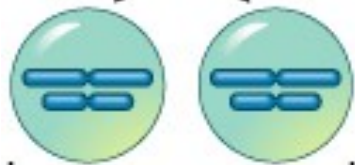
Possibilità 1



Metafase
della meiosi I



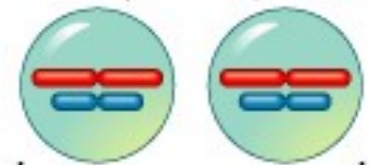
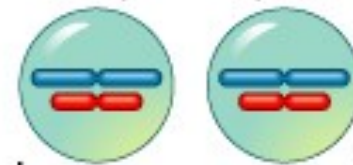
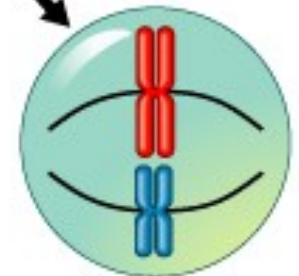
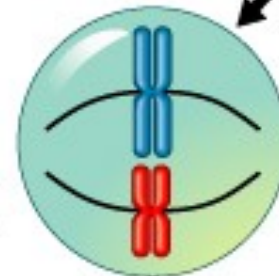
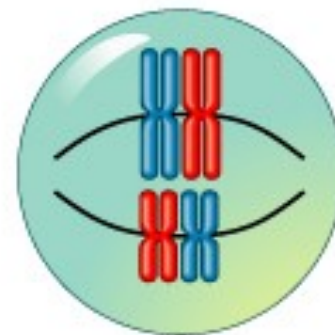
Metafase
della meiosi II



Gameti

Combinazione 1 **Combinazione 2**

Possibilità 2

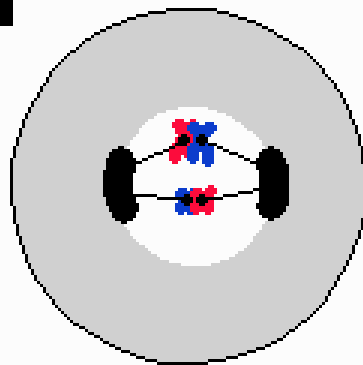
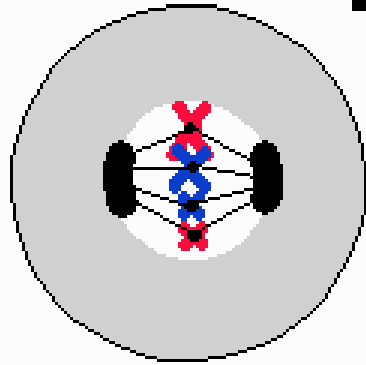


Combinazione 3 **Combinazione 4**

Mitosis

Meiosis I

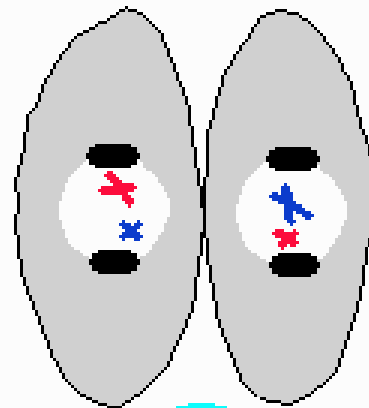
4N



A

Meiosis II

2N

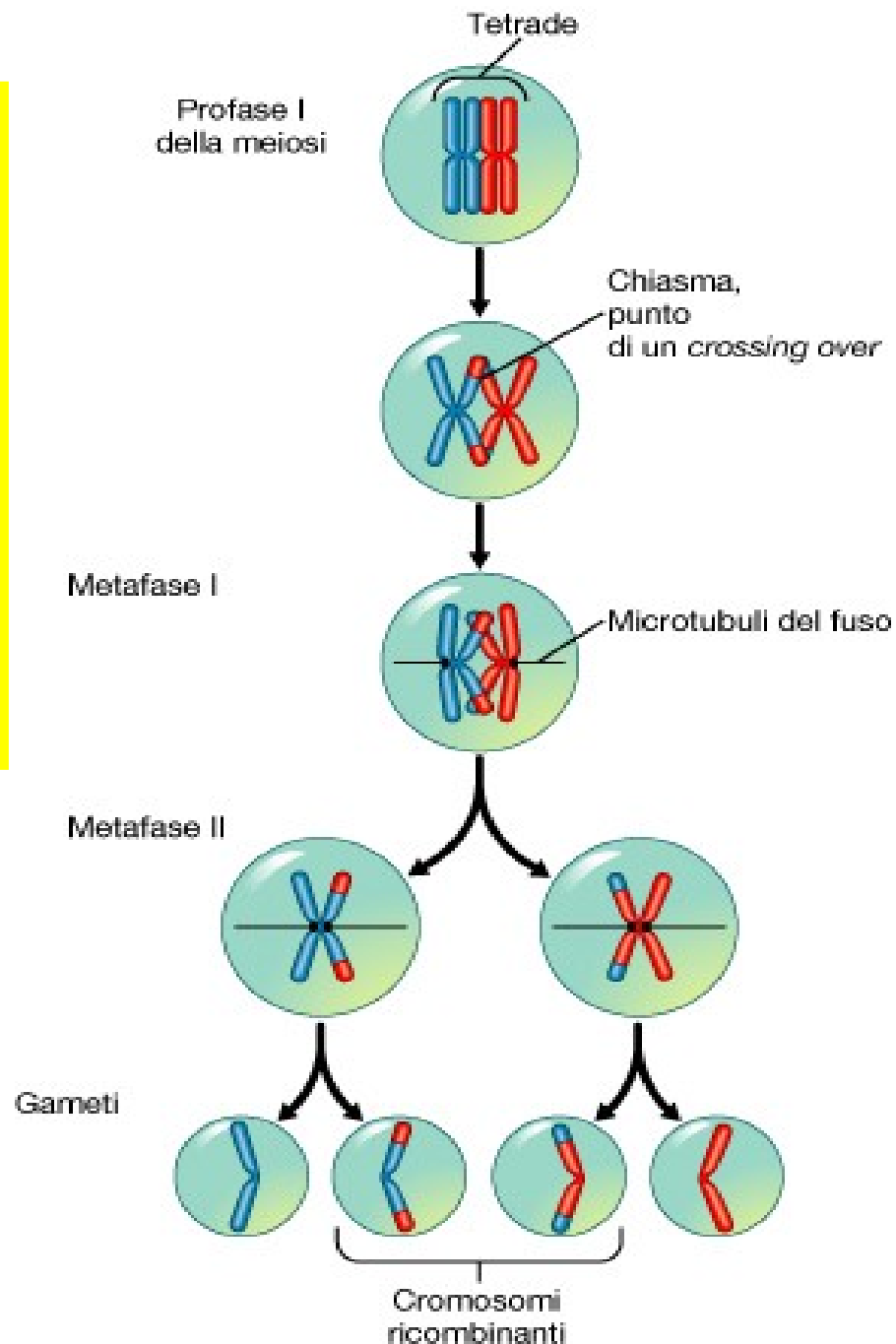
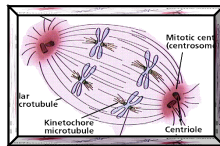


C

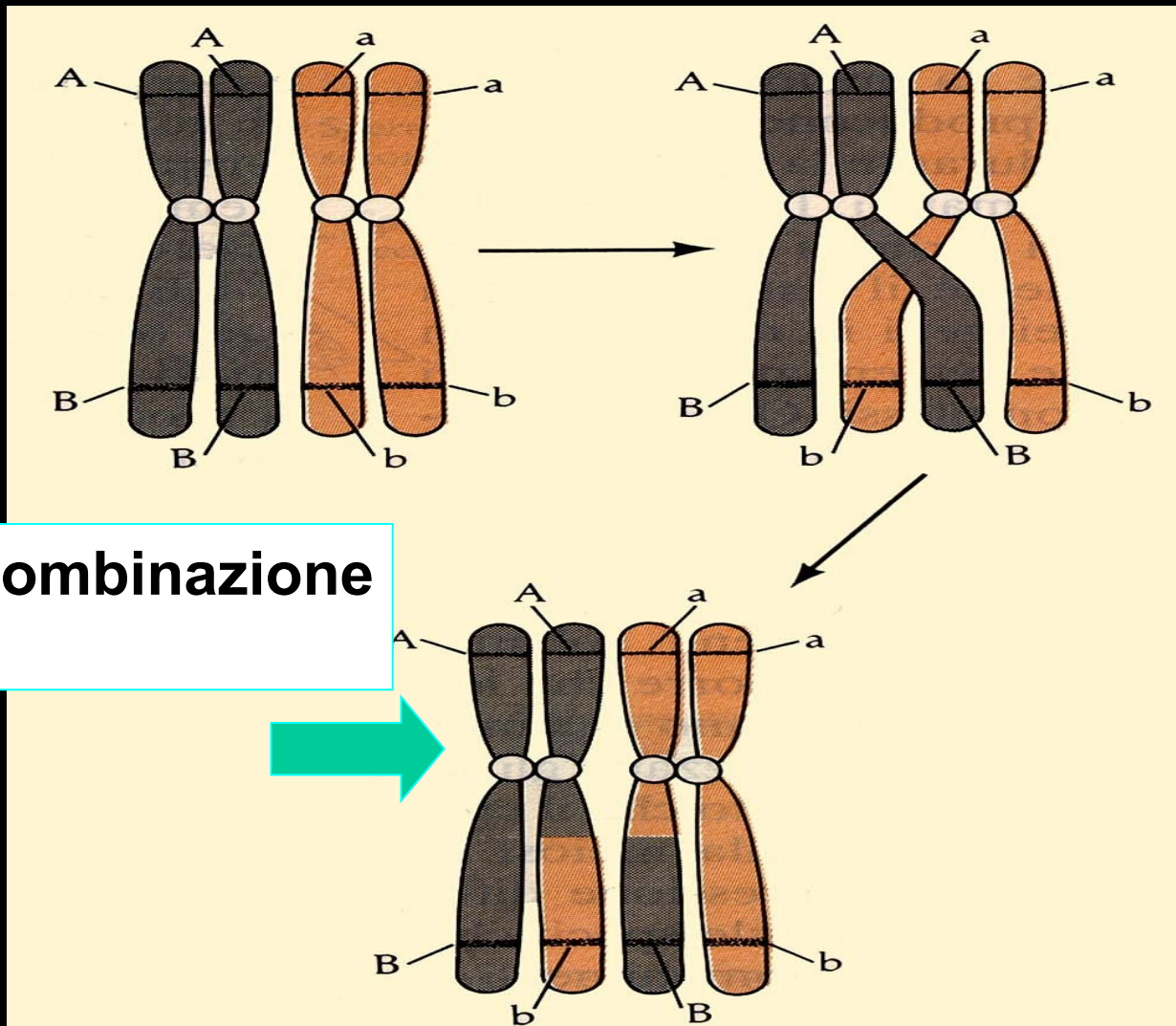
Conseguenze dell'assortimento indipendente dei cromosomi

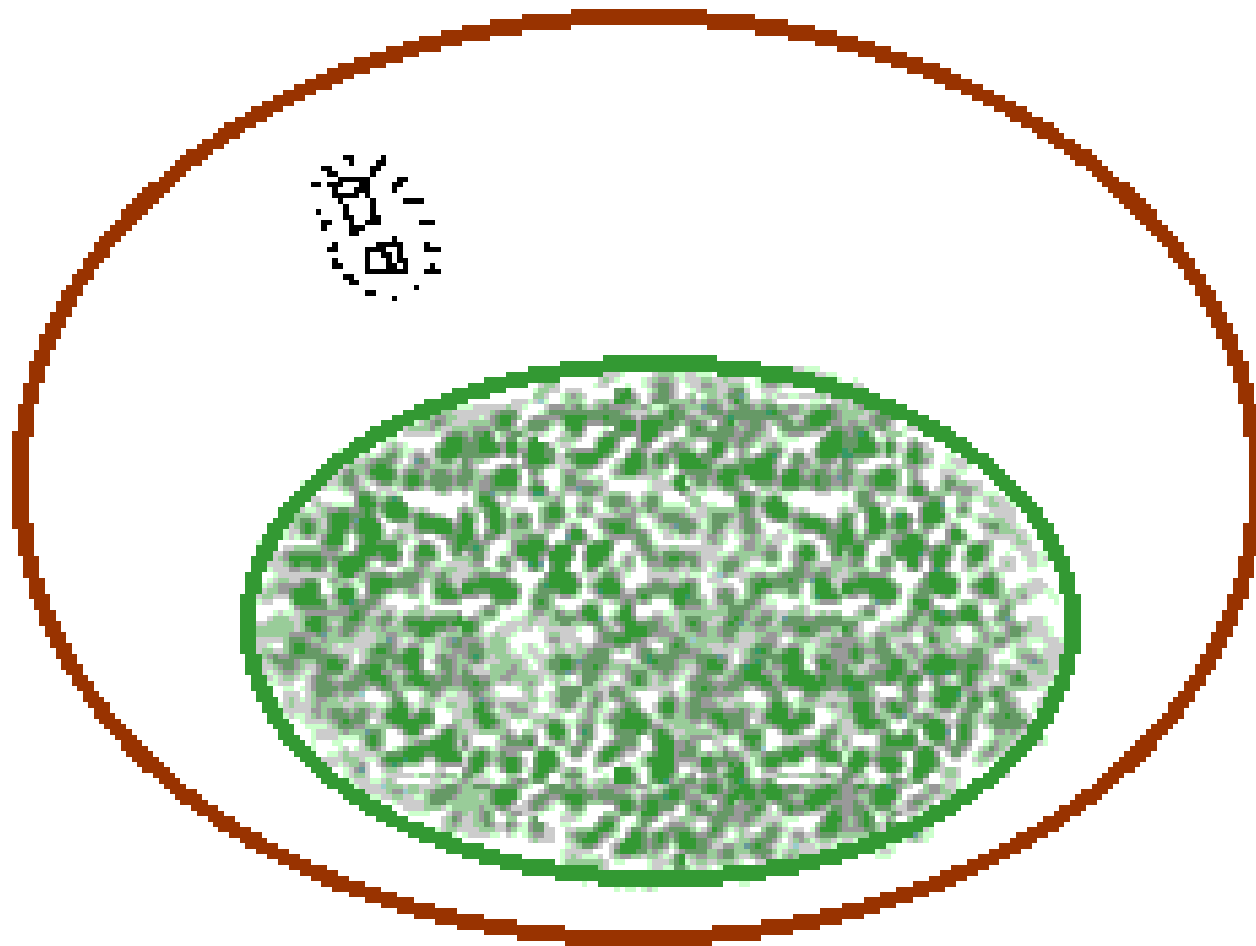
- In ogni specie, il numero totale di combinazioni cromosomiche possibili è 2^n , con n uguale al corredo aploide.
- Nell'uomo ($n = 23$) ci sono quindi 2^{23} (**8 milioni**) possibili combinazioni cromosomiche.
- Dal momento che spermatozoi e uova si fondono a caso, è perciò possibile la formazione di **64 miliardi** di zigoti diversi.

Il processo del *crossing-over*, che avviene durante la profase meiotica, aumenta notevolmente la variabilità genetica dei gameti che si formeranno, riassortendo i geni di origine paterna e materna dei cromosomi omologhi.

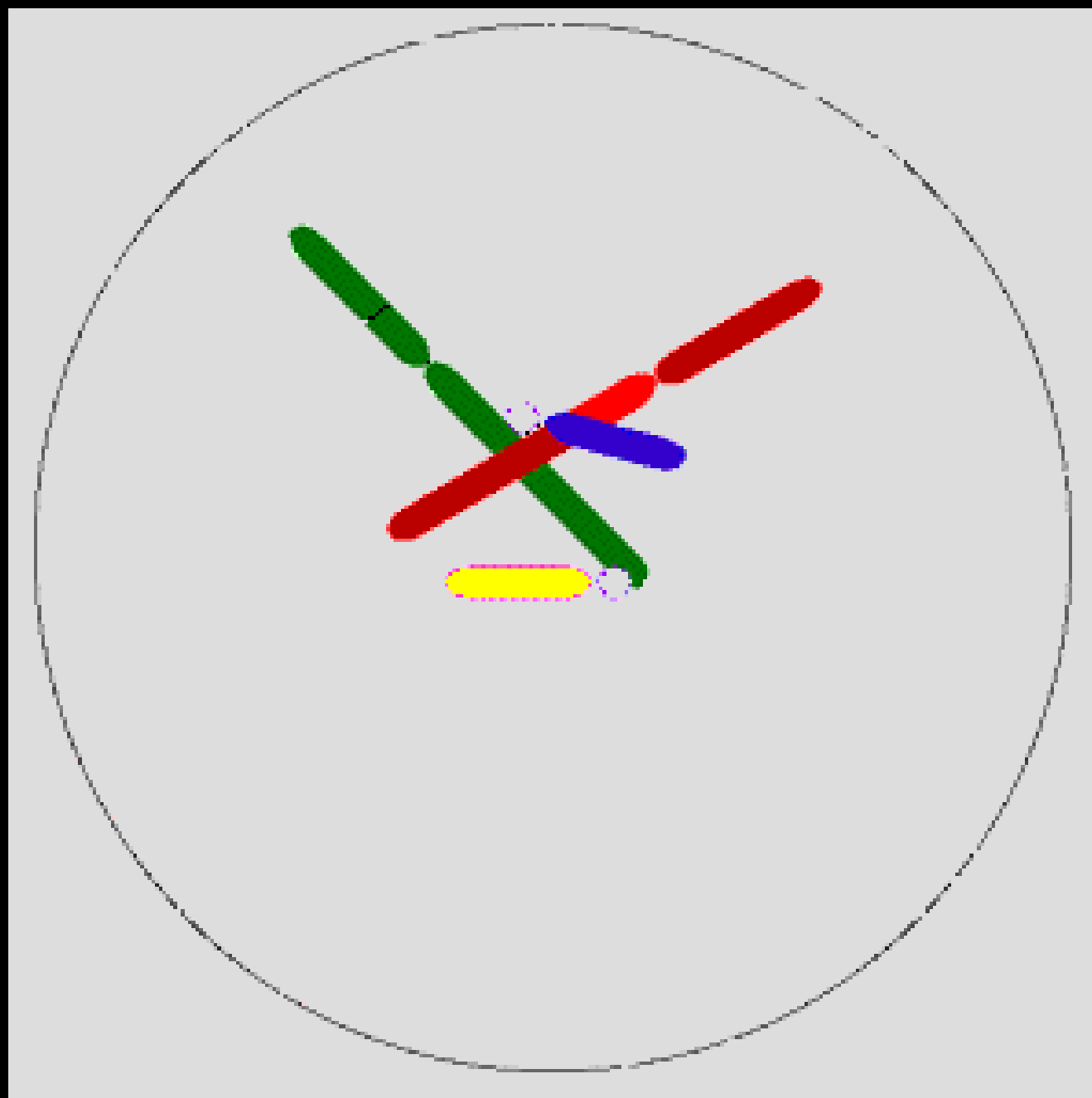


La ricombinazione genetica (crossing over)

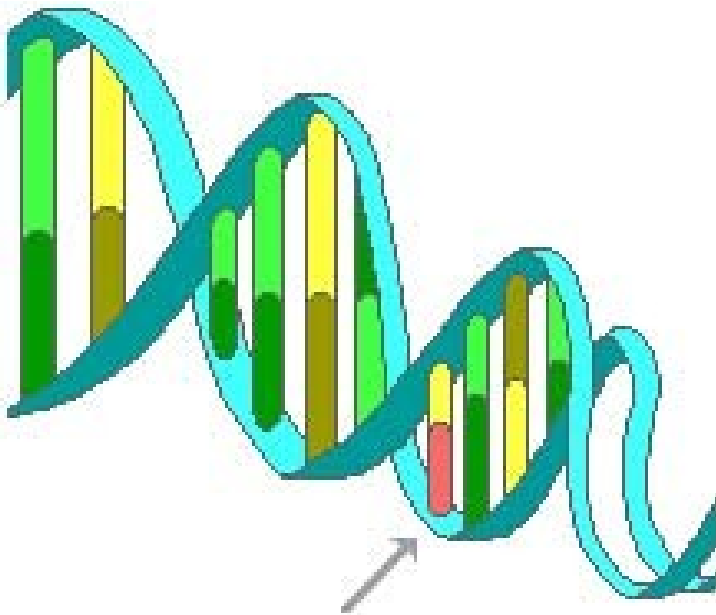




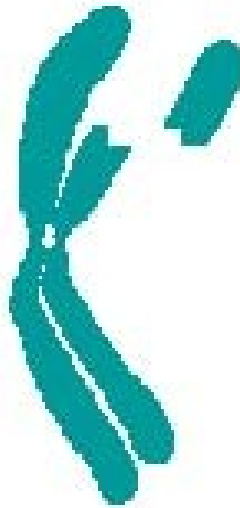
Description of the meiosis



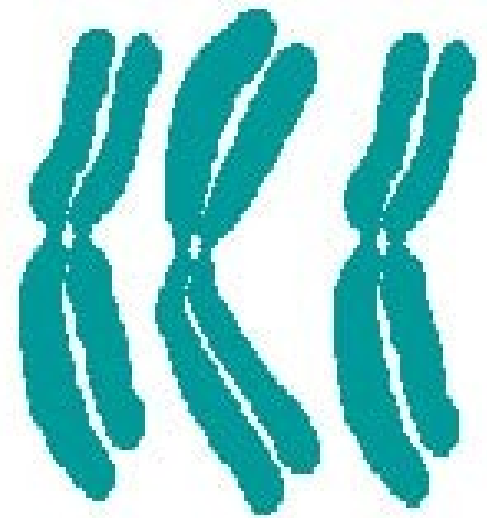
Le mutazioni



Mutazione
puntiforme

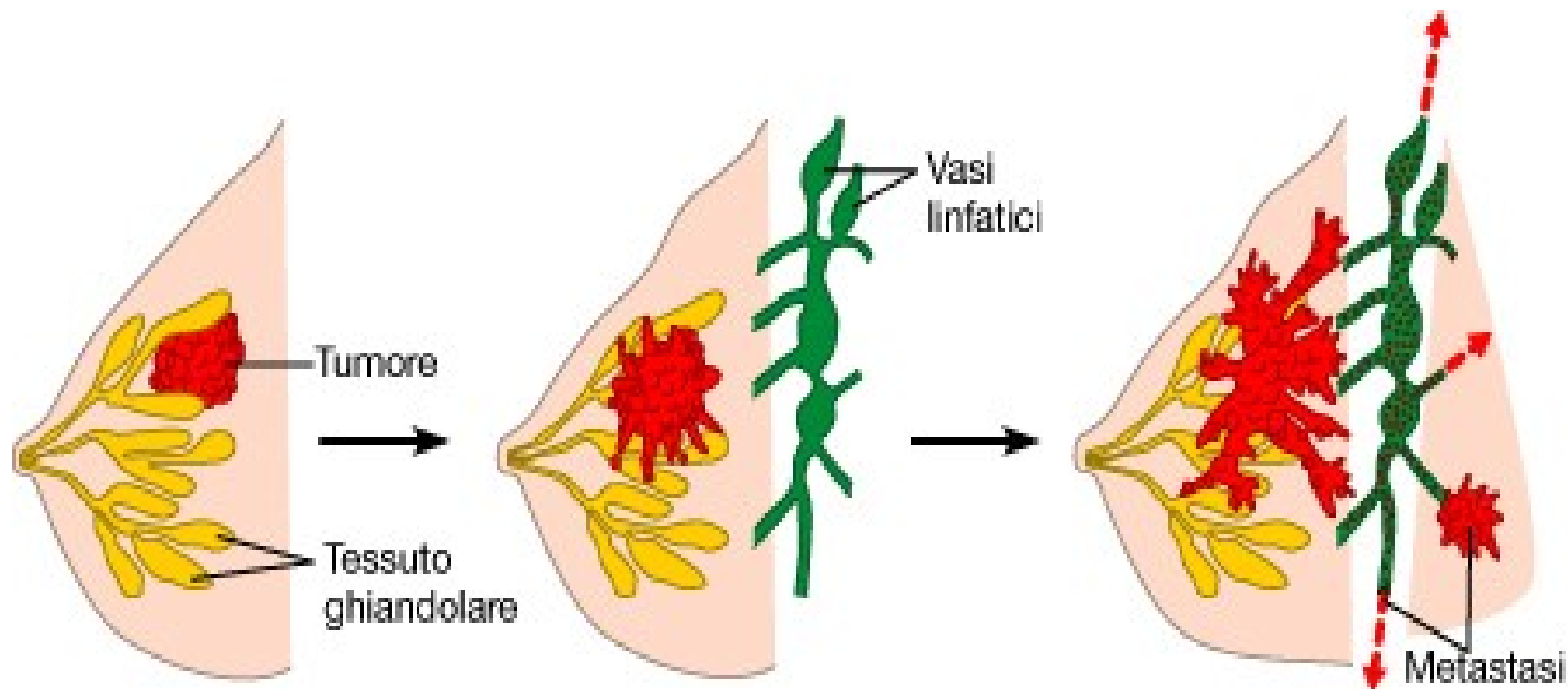


Mutazione
strutturale



Mutazione
numerica

Si è stimato che nell'uomo vengano prodotte circa 120 nuove mutazioni per generazione



Un tumore si accresce da una singola cellula cancerosa

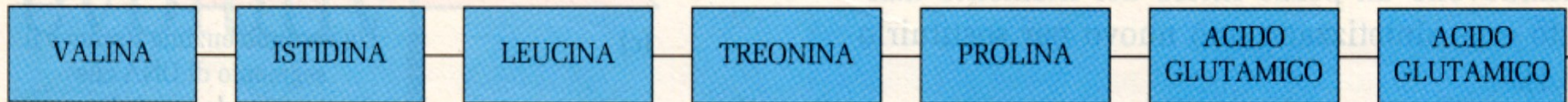
Le cellule cancerose invadono i tessuti circostanti

Le cellule cancerose diffondono attraverso i vasi linfatici ed ematici per raggiungere altre parti del corpo

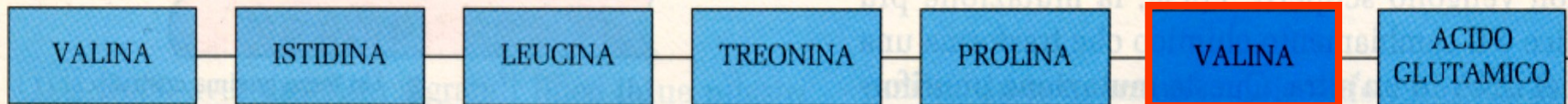
Tra le cause scatenanti di moltissimi tumori ci sono mutazioni di uno o più geni regolatori della crescita cellulare

Mutazioni puntiformi

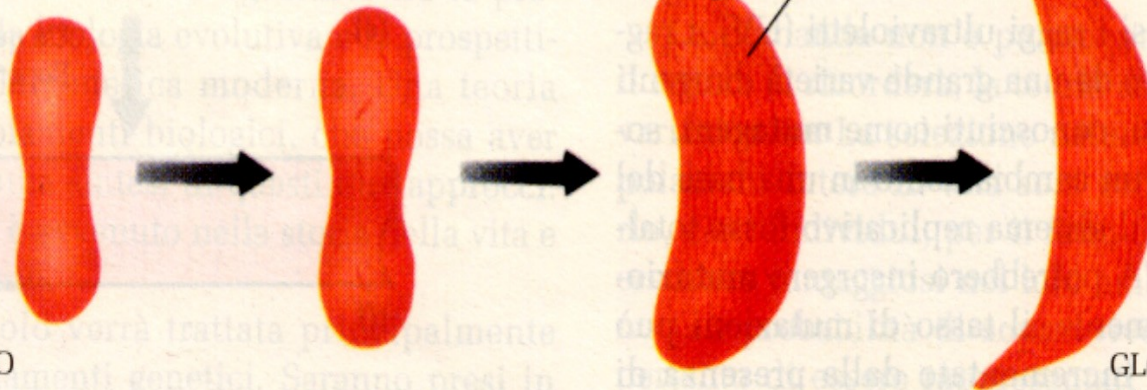
NORMALE



ANEMIA
FALCIFORME



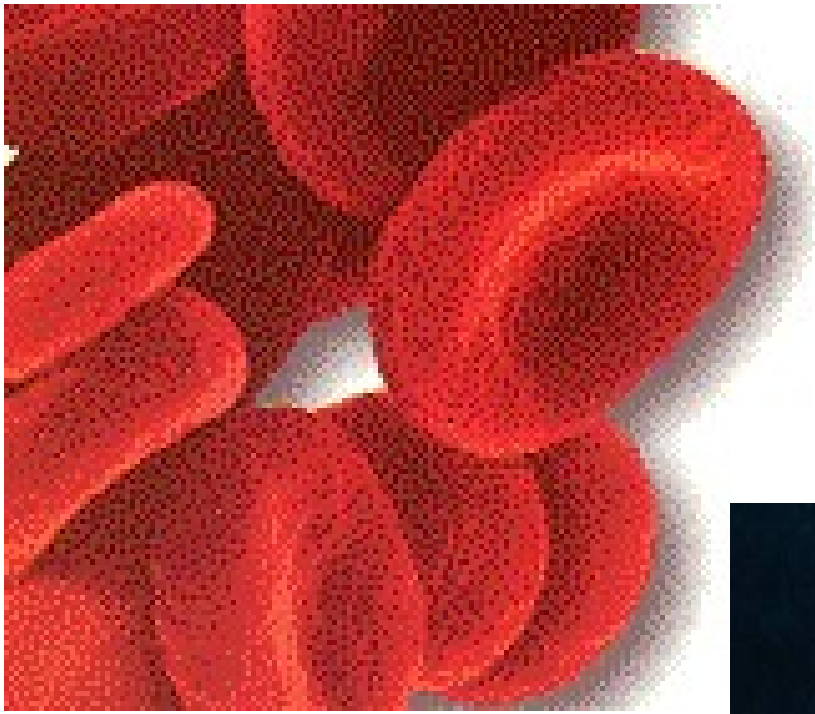
(a)



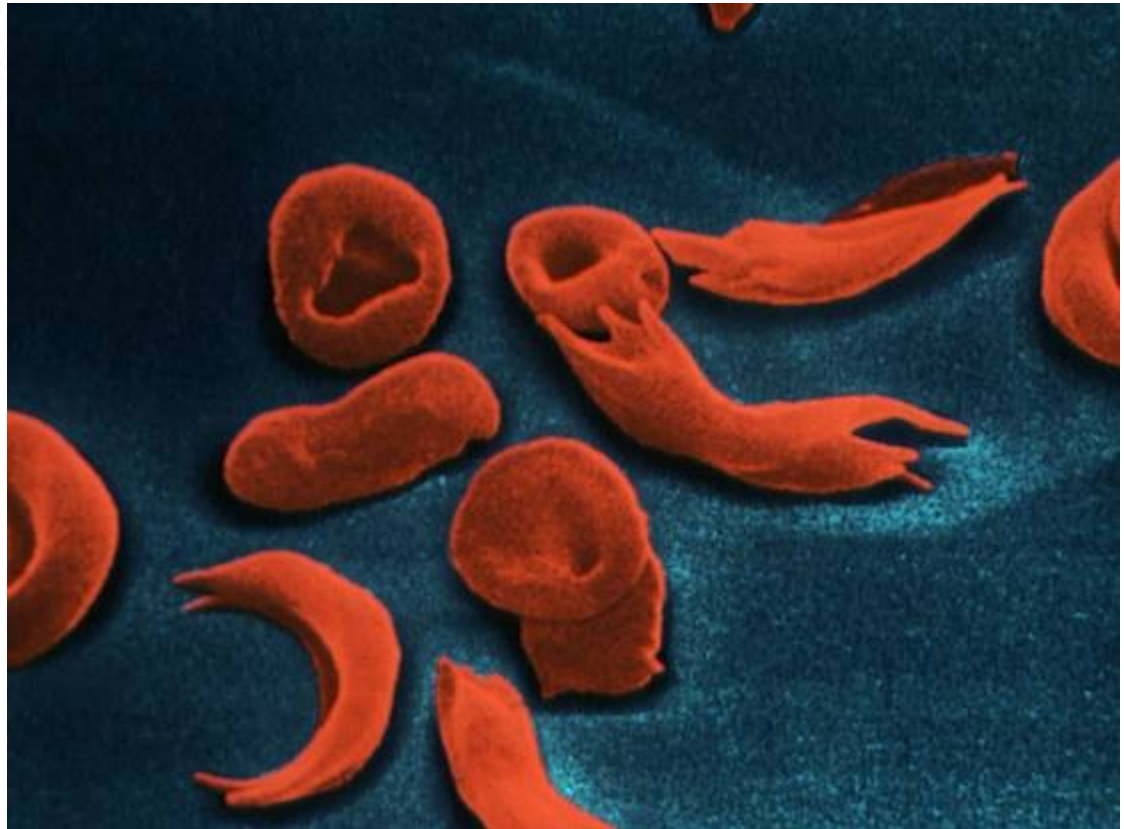
GLOBULO ROSSO
NORMALE

GLOBULO ROSSO
FALCIFORME

Globuli rossi normali



Globuli rossi
falciformi



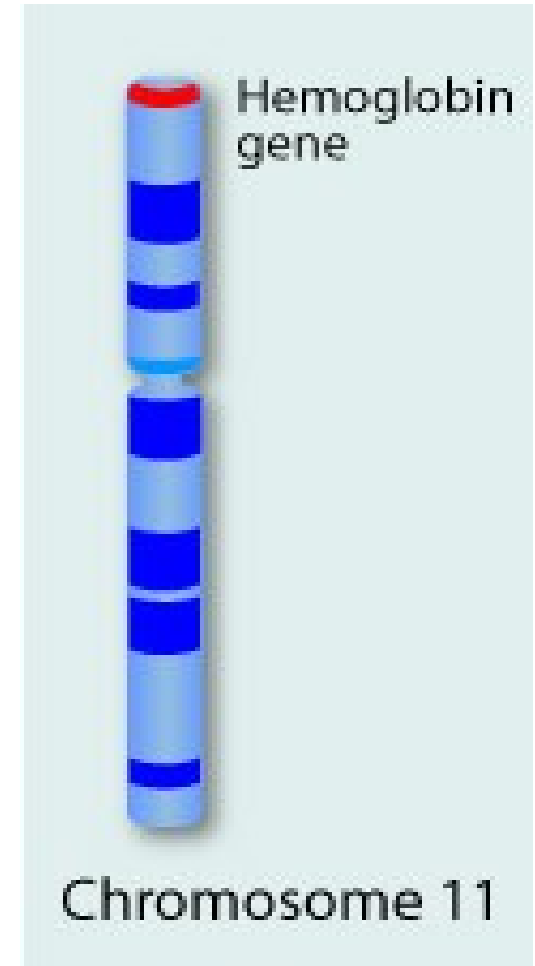
L'anemia falciforme

L'anemia falciforme è una malattia che colpisce i globuli rossi, che utilizzano una proteina chiamata **emoglobina** per il trasporto di ossigeno e anidride carbonica nel sangue.

Normalmente, i globuli rossi sono di forma lenticolare e sufficientemente elastici da poter passare attraverso i capillari sanguigni.

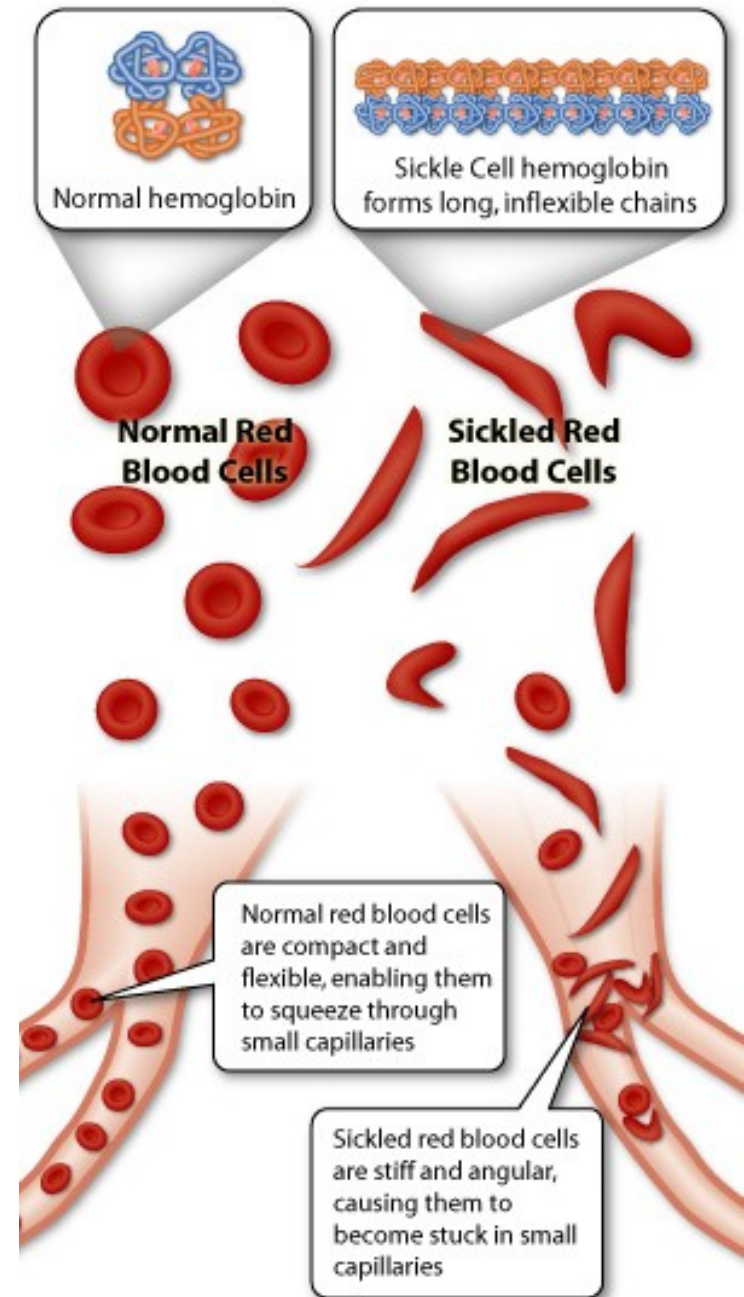
La molecola dell'emoglobina è formata da due subunità, una denominata **alfa** e l'altra **beta**

Le persone affette da anemia falciforme presentano una **mutazione puntiforme in un gene del cromosoma 11** che codifica per la subunità **beta** dell'emoglobina.



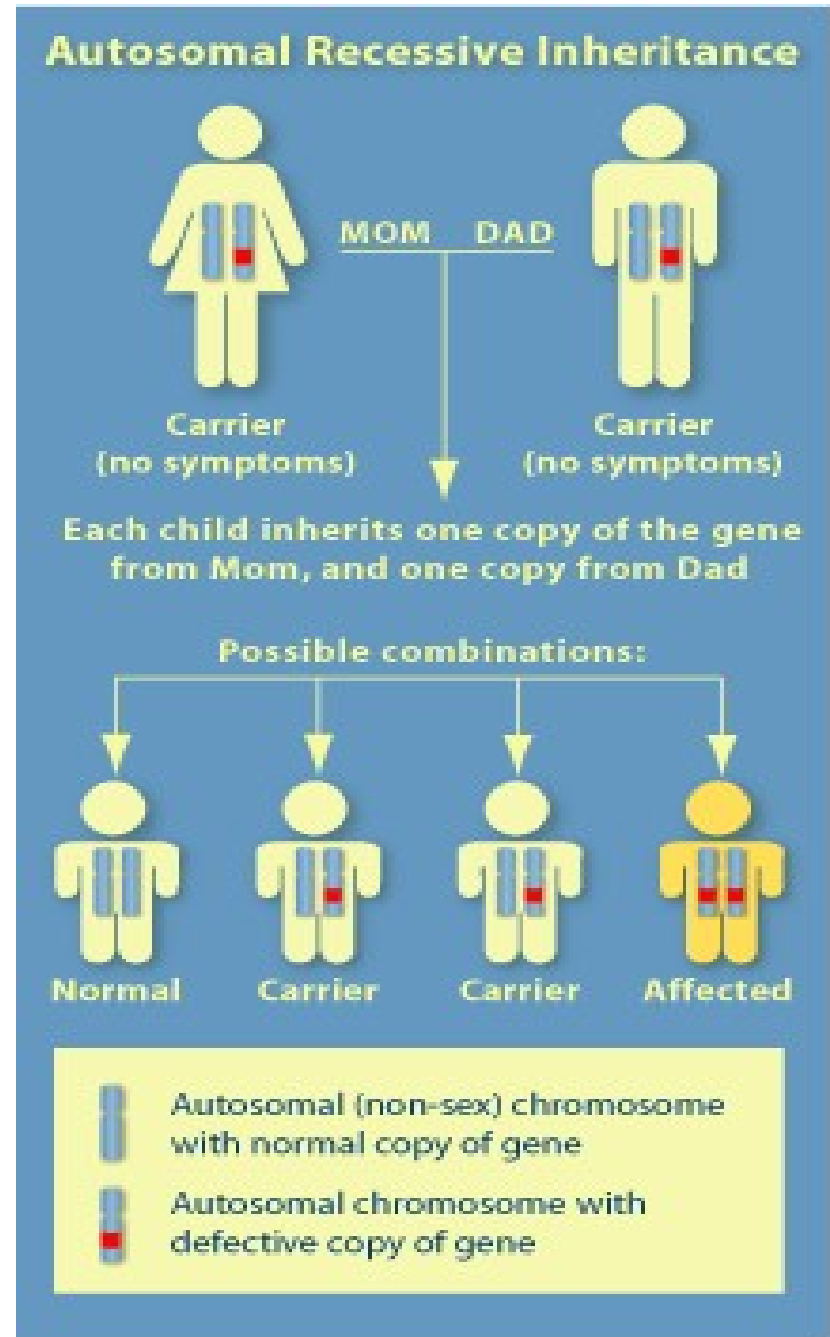
L'anemia falciforme

- Nelle persone affette da anemia falciforme, ***le molecole di emoglobina non si formano correttamente***, determinando ***rigidità e forma a mezzaluna*** dei globuli rossi.
- Questi globuli rossi difettosi ***ostruiscono i piccoli vasi sanguigni*** e sono incapaci di trasportare efficacemente ossigeno e anidride carbonica, ***provocando dolore e danni agli organi***.
- Diversamente da quelli normali, i globuli rossi difettosi vivono dai 10 ai 20 giorni, anziché 120.



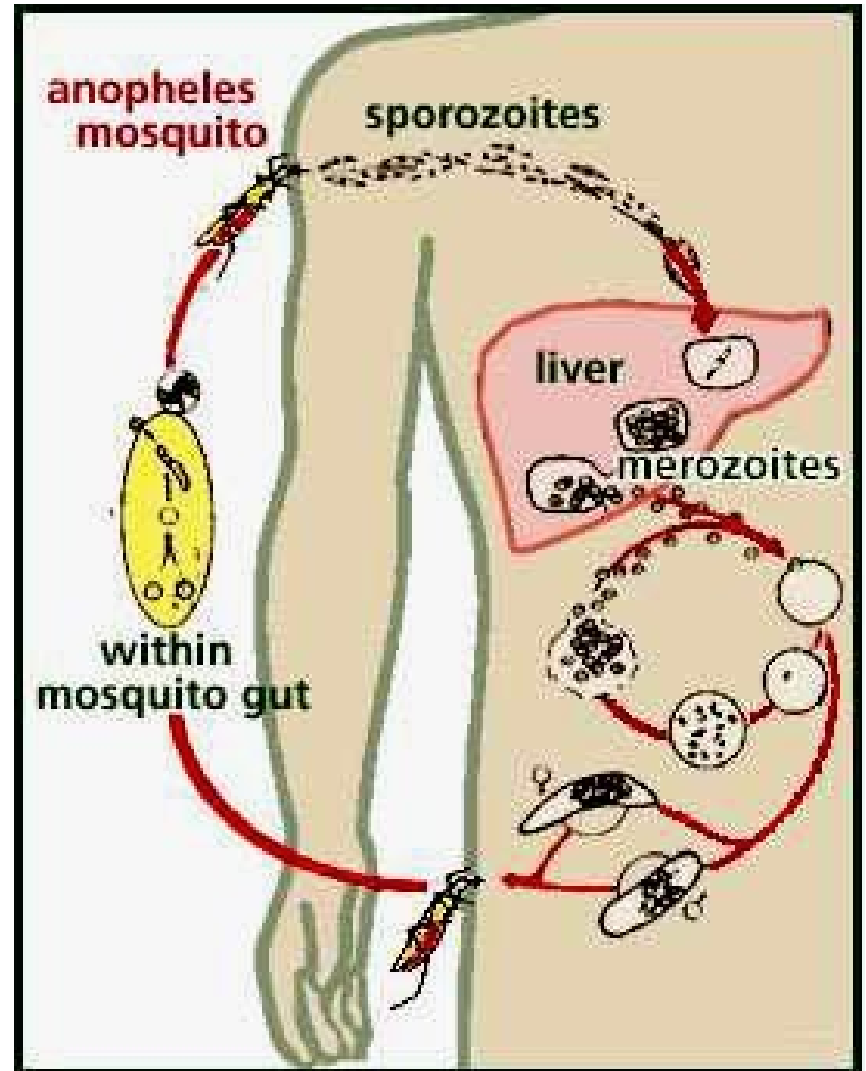
L'anemia falciforme

- La malattia si eredita come ***pattern autosomico recessivo***.
- Questo significa che un bambino non erediterà la malattia, a meno che entrambi i genitori non gli trasmettano una copia difettosa del gene.
- ***Gli individui che ereditano una sola copia difettosa del gene***, sono portatori della malattia.
- Essi ***sono clinicamente normali***, ma possono trasmettere alla prole il gene difettoso.



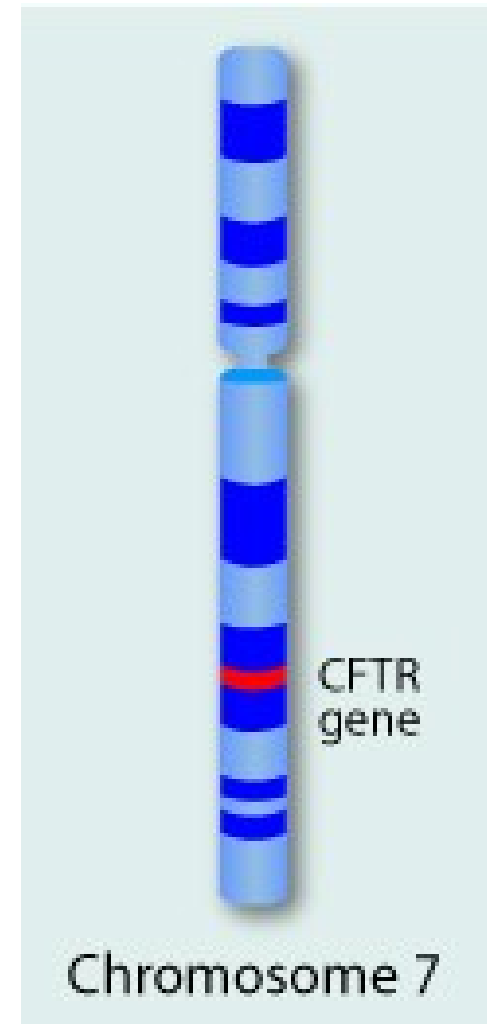
L'anemia falciforme protegge dalla malaria

- In the United States, ***the disease most commonly affects African-Americans***. About 1 out of every 500 African-American babies born in the United States has sickle cell anemia.
- Sickle cell disease is most common among people from Africa, India, the Caribbean, the Middle East, and the Mediterranean.
- The high prevalence of the defective gene in these regions may be due to the fact that ***carriers of a mutation in the beta-subunit of hemoglobin are more resistant to malaria***.
- ***Malaria*** is a disease ***caused by a parasite that lives in red blood cells*** and is transmitted to a person when they are bitten by an infected mosquito. The sometimes fatal disease is common in hot countries, and causes recurring chills and fever.



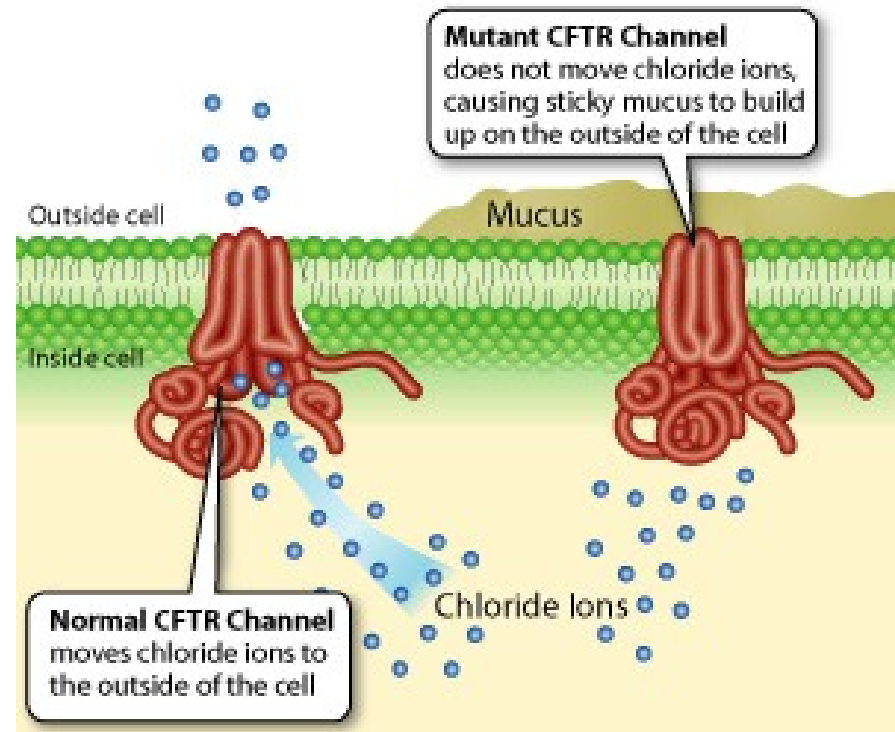
La fibrosi cistica

- Cystic fibrosis is a genetic disorder that ***affects the respiratory and digestive systems***.
- People with cystic fibrosis inherit a ***defective gene on chromosome 7 called CFTR*** (cystic fibrosis transmembrane conductance regulator).
- The protein produced by this gene normally helps salt (sodium chloride) move in and out of cells.
- If the protein doesn't work correctly, that movement is blocked and ***an abnormally thick sticky mucous is produced*** on the outside of the cell.
- ***The cells most seriously affected by this are the lung cells.*** This mucous clogs the airways in the lungs, and increases the risk of infection by bacteria.



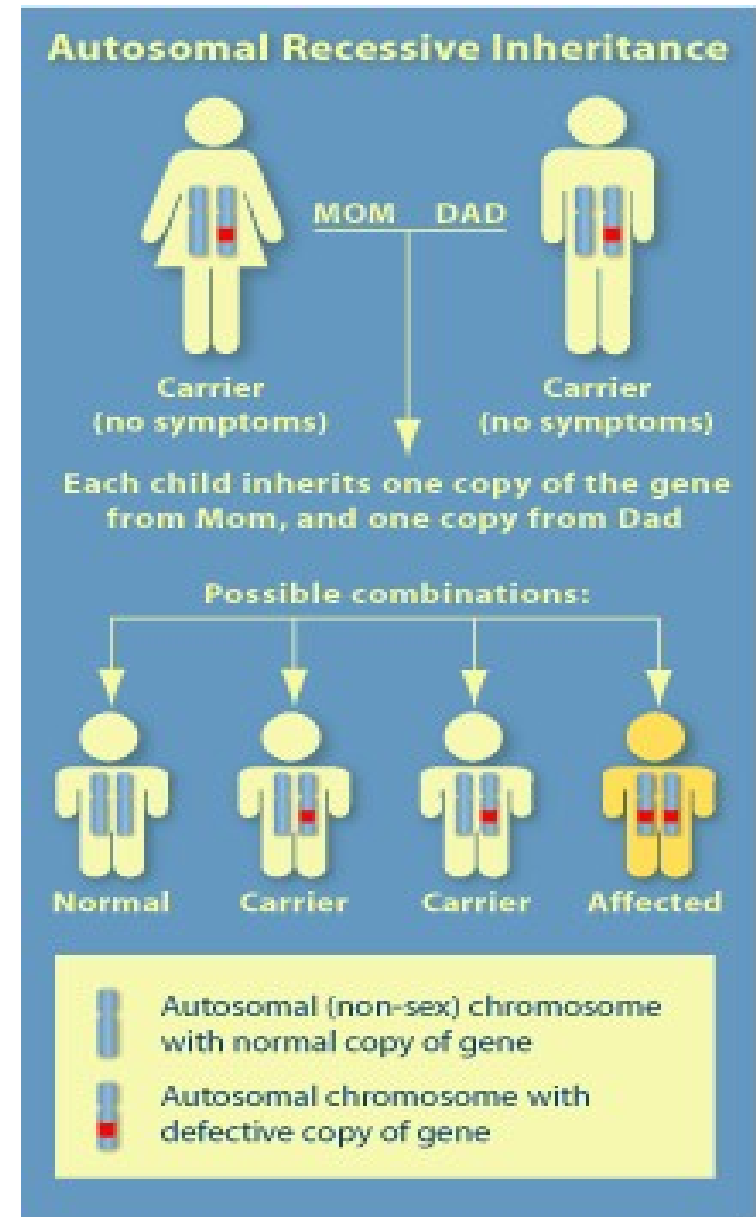
La fibrosi cistica

- The thick mucous also ***blocks ducts in the pancreas***, so digestive enzymes can't get into the intestine.
- Without these enzymes, the intestine ***cannot properly digest food***.
- People who have the disorder often do not get the nutrition they need to grow normally.
- Finally, cystic fibrosis ***affects the sweat glands***.
- ***Too much salt is lost through sweat***, which can disrupt the delicate balance of minerals in the body.



La fibrosi cistica

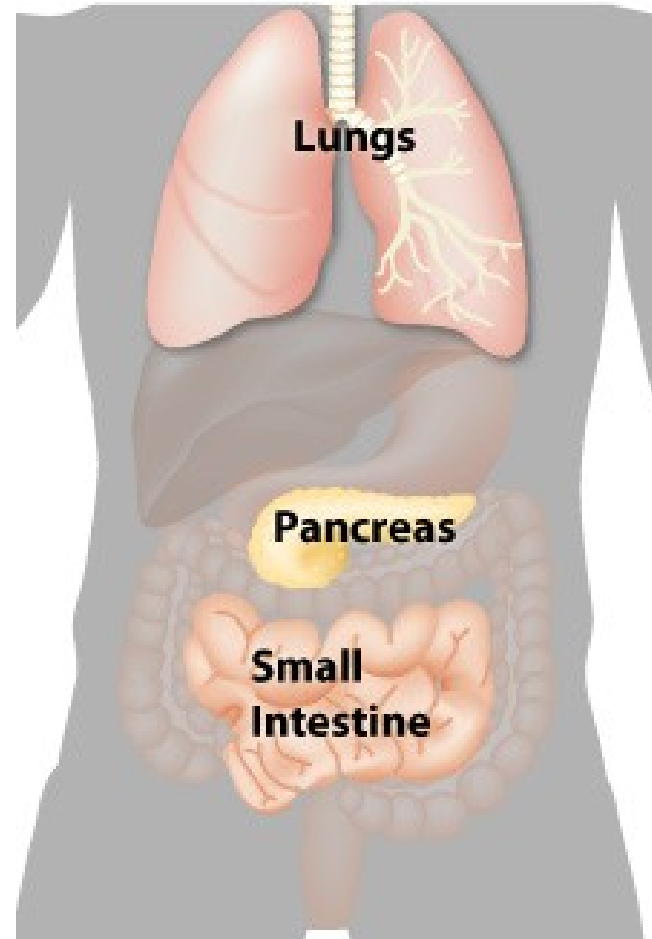
- Cystic fibrosis *is a recessive disorder*, which means that ***both parents must pass on the defective gene*** for any of their children to get the disease.
- If a child inherits only one copy of the faulty gene, he or she will be a carrier. Carriers don't actually have the disease, but they can pass it on to their children.
- Symptoms of cystic fibrosis can include:
 - coughing or wheezing
 - respiratory illnesses
 - weight loss
 - salty-tasting skin
- Most cystic fibrosis patients only live to be slightly more than thirty years old.



La fibrosi cistica

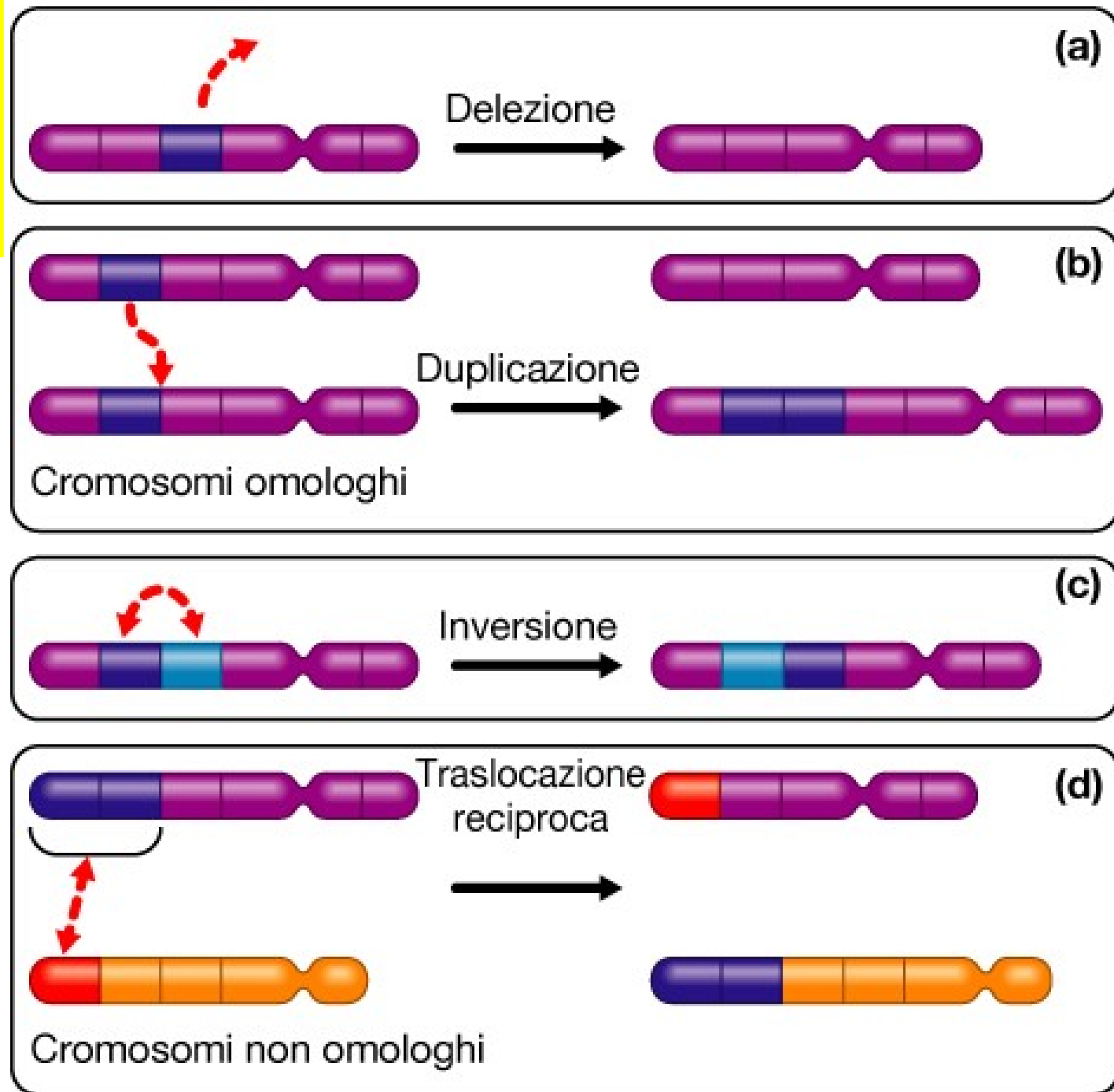
- ***More than 1,000 different mutations in the CFTR gene*** have been identified in cystic fibrosis patients.
- ***The most common mutation*** (observed in 70% of cystic fibrosis patients) ***is a three-base deletion in the DNA sequence***, causing an ***absence of a single amino acid in the protein product***.
- ***Gene therapy*** (a treatment currently in clinical trials), in which ***the healthy CFTR gene is inserted into the lung cells*** of a patient to correct the defective gene.

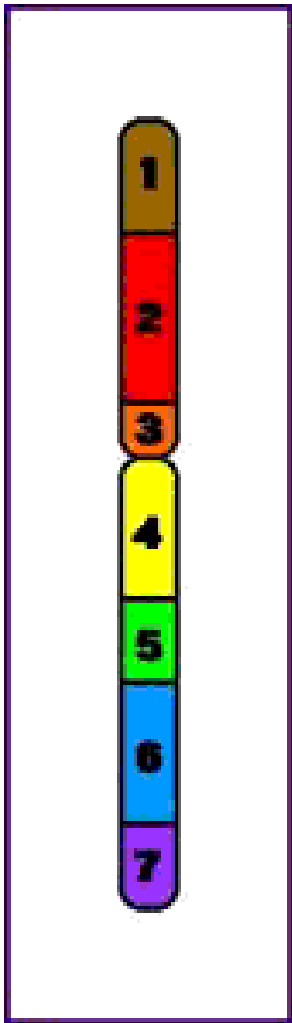
Organs Affected by Cystic Fibrosis



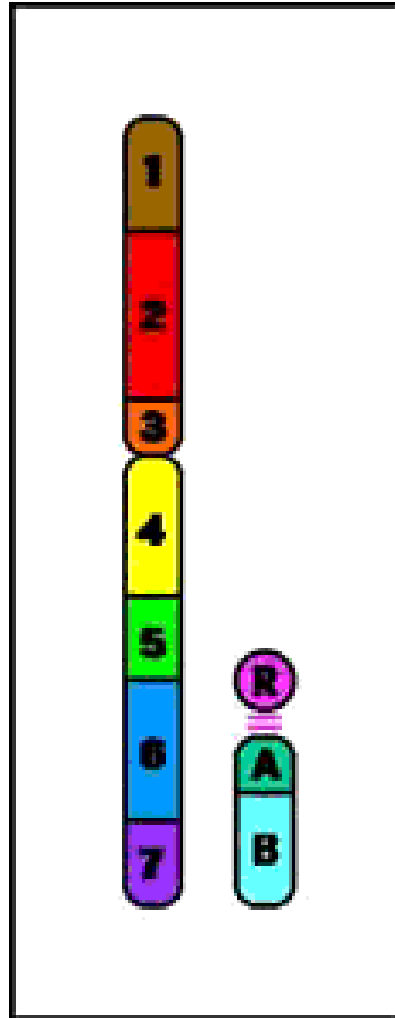
Molte mutazioni interessano la struttura dei cromosomi

Da: Campbell-Reece "L'essenziale di biologia", Zanichelli Ed.

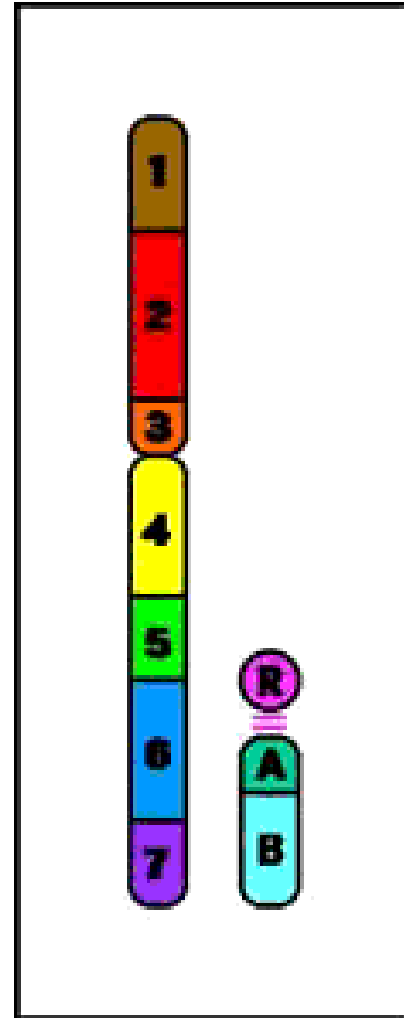


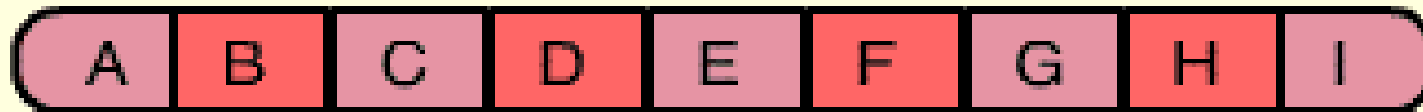


Delezione



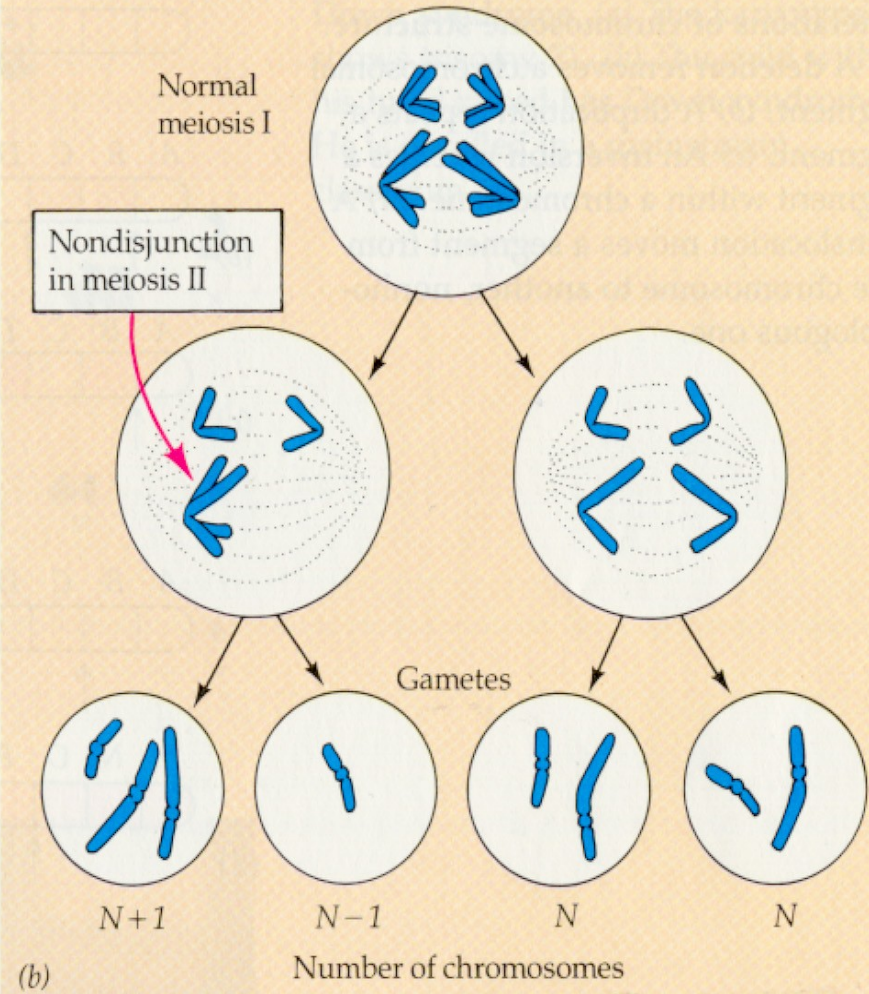
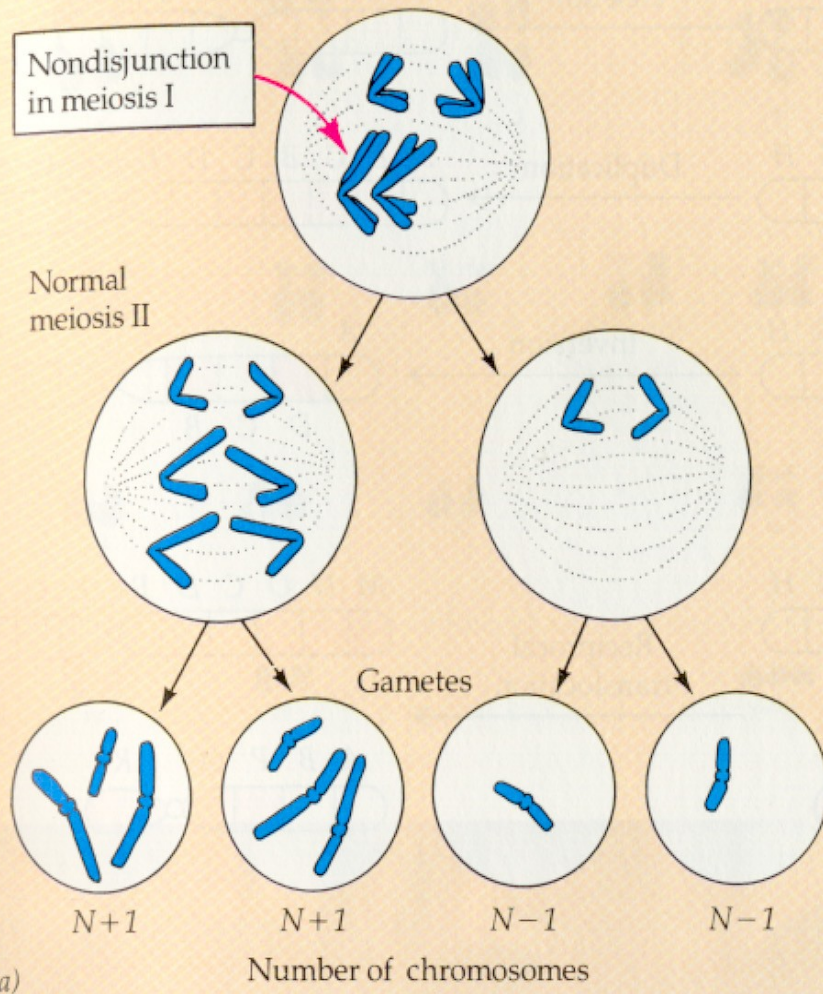
Traslocazione





1. Original

Altre mutazioni interessano il numero dei cromosomi e sono causate da difetti del processo meiotico



Cellula
uovo

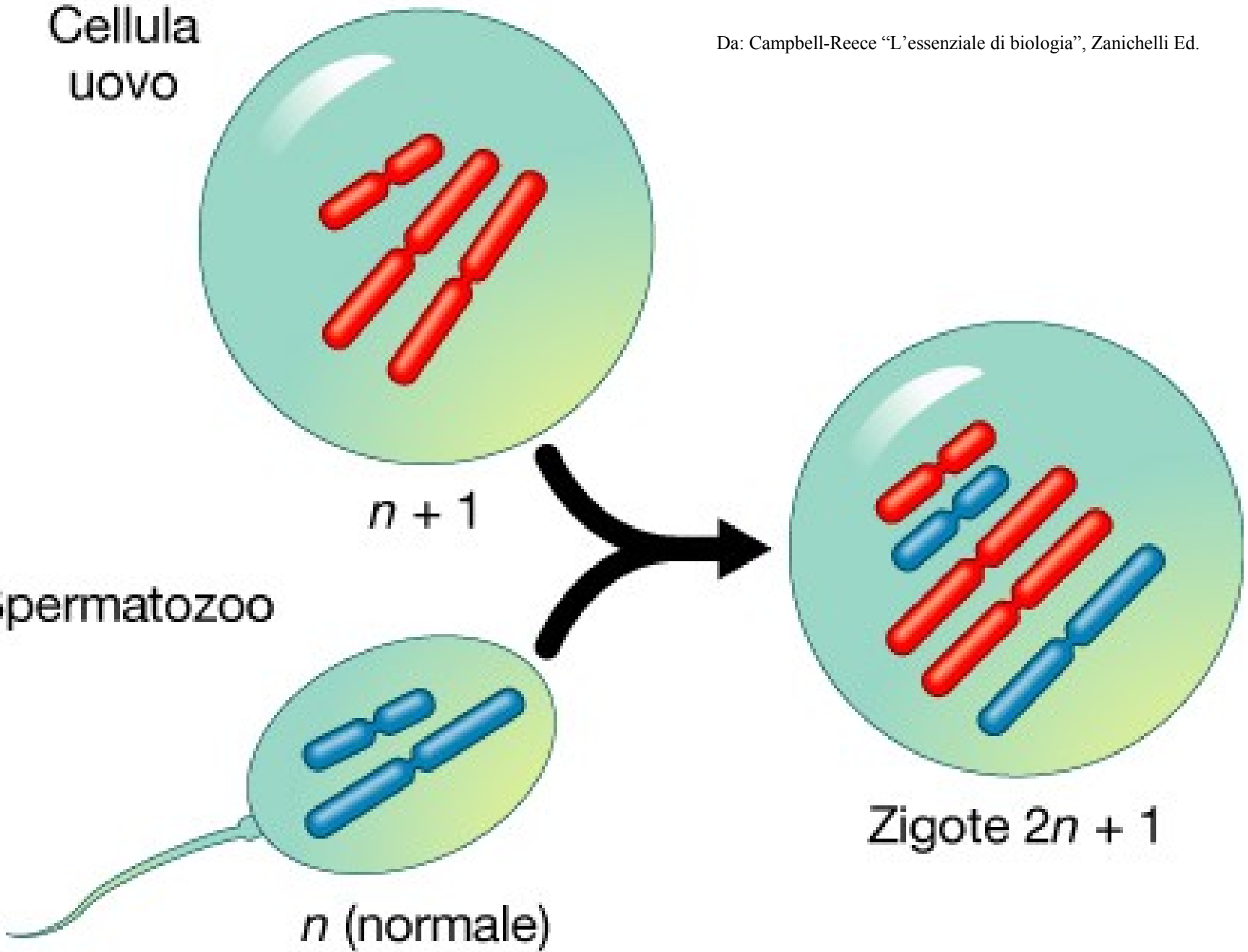
Da: Campbell-Reece "L'essenziale di biologia", Zanichelli Ed.

$n + 1$

Spermatozoo

n (normale)

Zigote $2n + 1$





Da: Campbell-Reece "L'essenziale di biologia", Zanichelli Ed.

Le mutazioni numeriche dei cromosomi possono dare origine a varie *sindromi*

Sindrome di Down (trisomia 21)

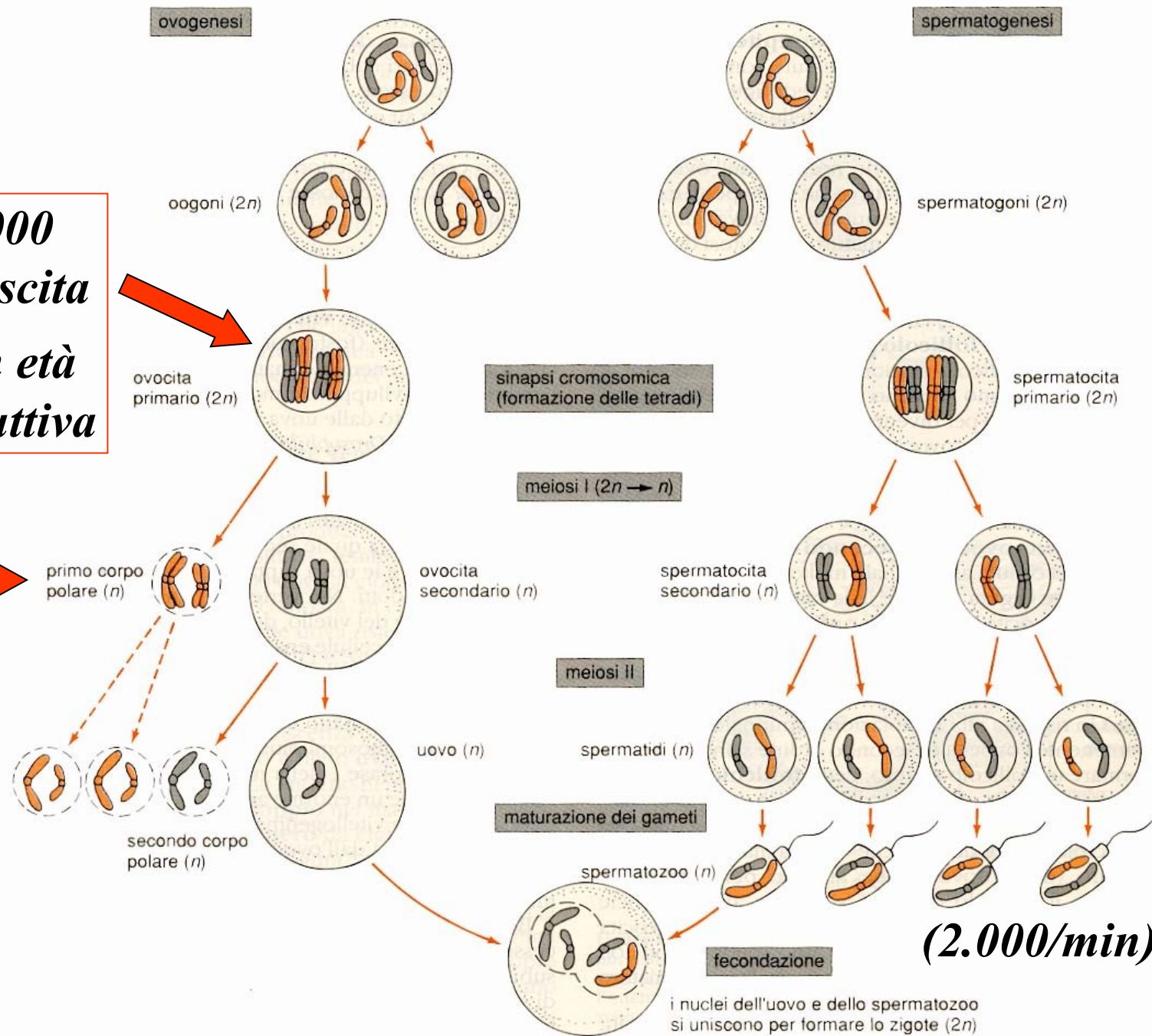
- It affects *1/800* to *1/1,000 babies*.
- People with Down syndrome have very distinct facial features: a ***flat face***, a ***small broad nose***, ***abnormally shaped ears***, a ***large tongue***, and ***upward slanting eyes*** with small folds of skin in the corners.
- People with Down syndrome have an increased risk of developing a number of medically significant problems:
 - respiratory infections
 - gastrointestinal tract obstruction
 - leukemia
 - heart defects
 - hearing loss
 - hypothyroidism
 - various eye abnormalities
 - moderate to severe mental retardation (children with Down syndrome usually develop more slowly than their peers, and have trouble learning to walk, talk, and take care of themselves)
- Because of these medical problems most people with Down syndrome have a decreased life expectancy. About half live to be 50 years of age.

Bambini affetti da sindrome di Down (ogni 1000 nascite)

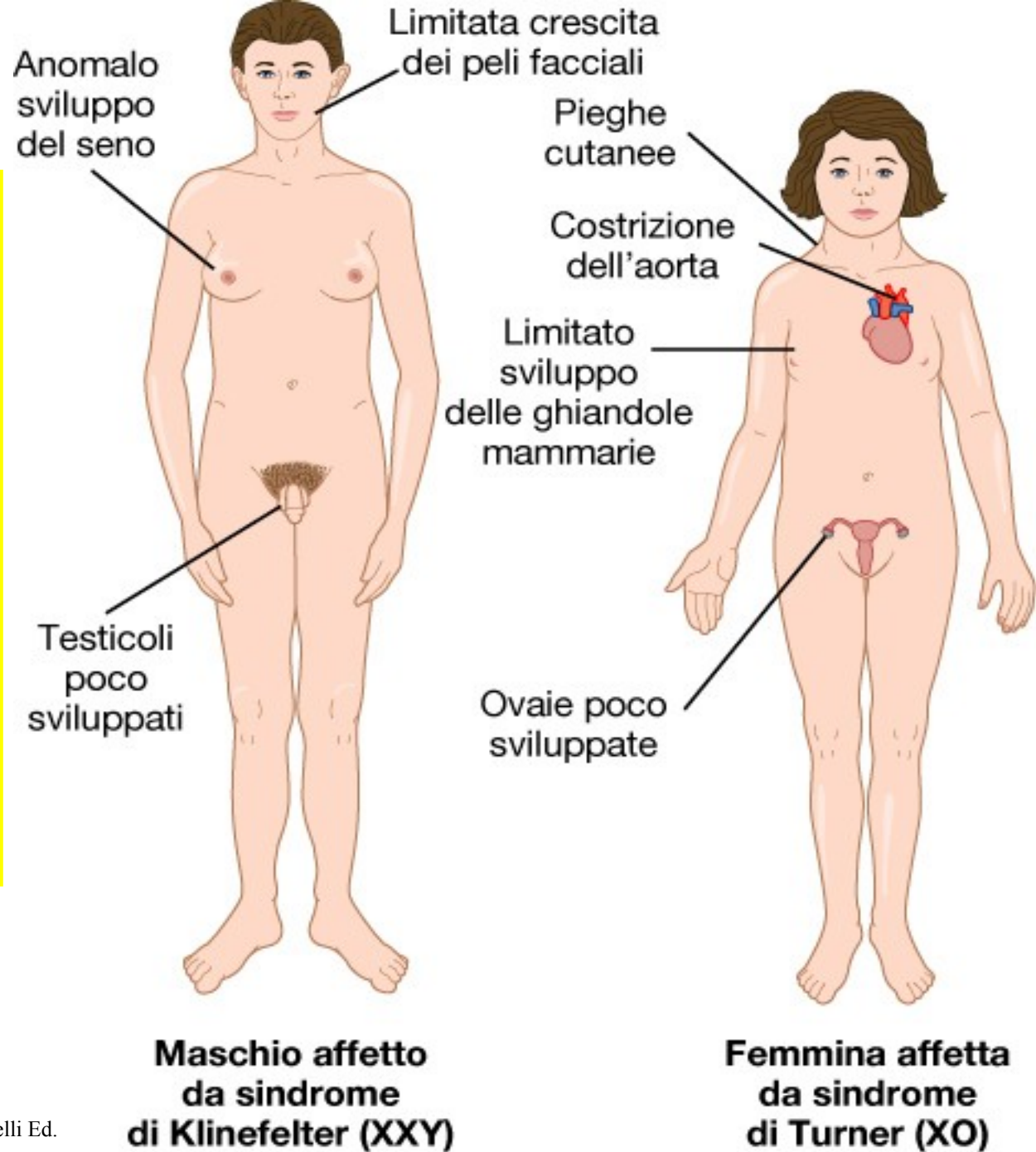
Tipicamente, la frequenza delle mutazioni caratterizzate da un numero anomalo di cromosomi sono direttamente correlate all'età dell'individuo riproduttore (maschio e/o femmina)



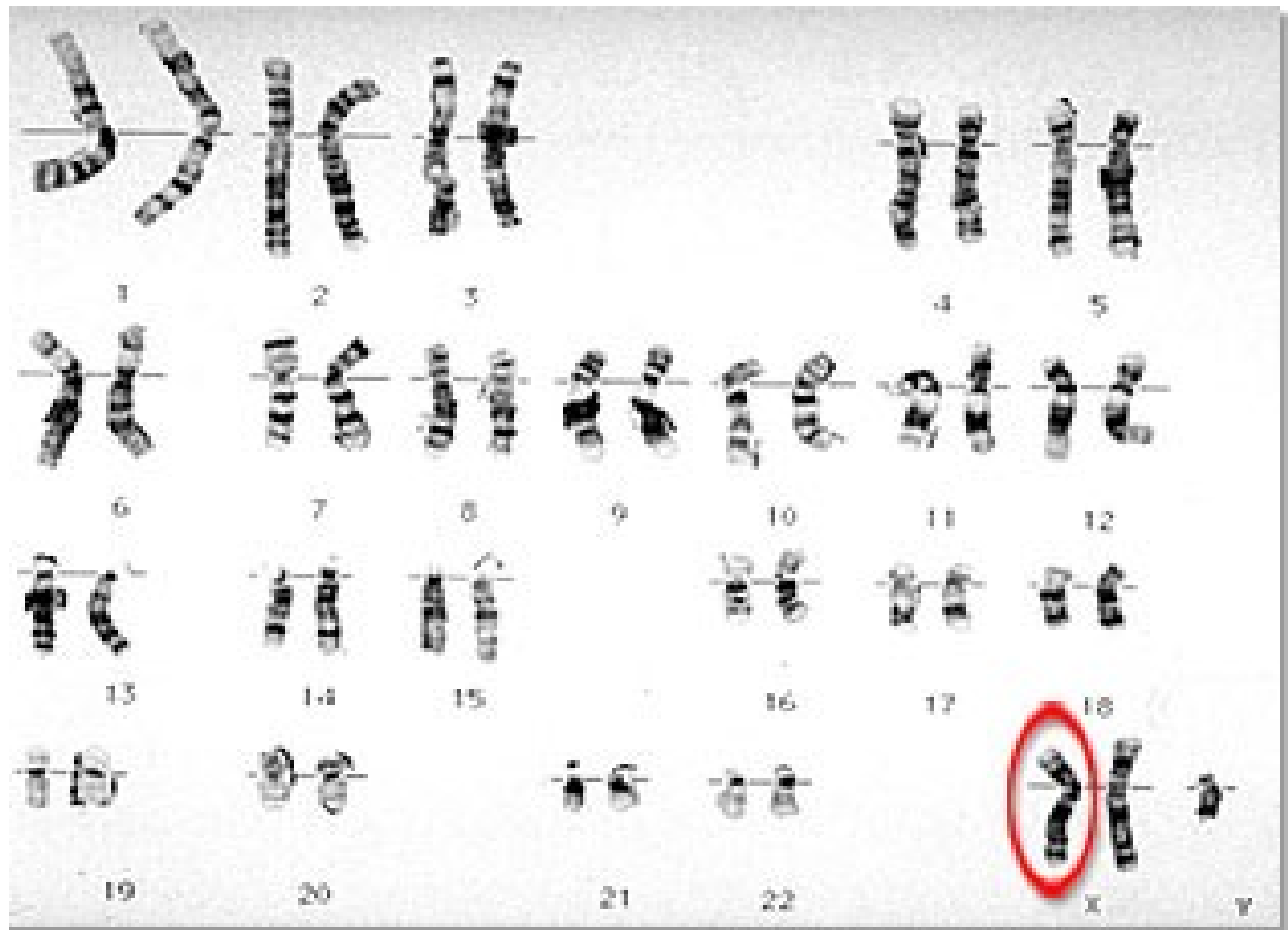
500.000
alla nascita
400 in età
riproduttiva



In molti casi di mutazioni numeriche dei cromosomi l'embrione non sopravvive. Nei casi in cui si abbia sopravvivenza, queste mutazioni determinano quasi sempre effetti deleteri nell'individuo adulto.



Sindrome di Klinefelter (XXY)



Sindrome di Klinefelter (XXY)

- It affects ***1/500*** to ***1/1,000*** males.
- People with this disorder ***develop as males*** with ***subtle characteristics*** that become ***apparent during puberty***.
- They are ***often tall*** and usually ***don't develop secondary sex characteristics***, such as facial hair or underarm and pubic hair.
- The extra X chromosome ***primarily affects the testes***, which produce sperm and the male hormone testosterone.

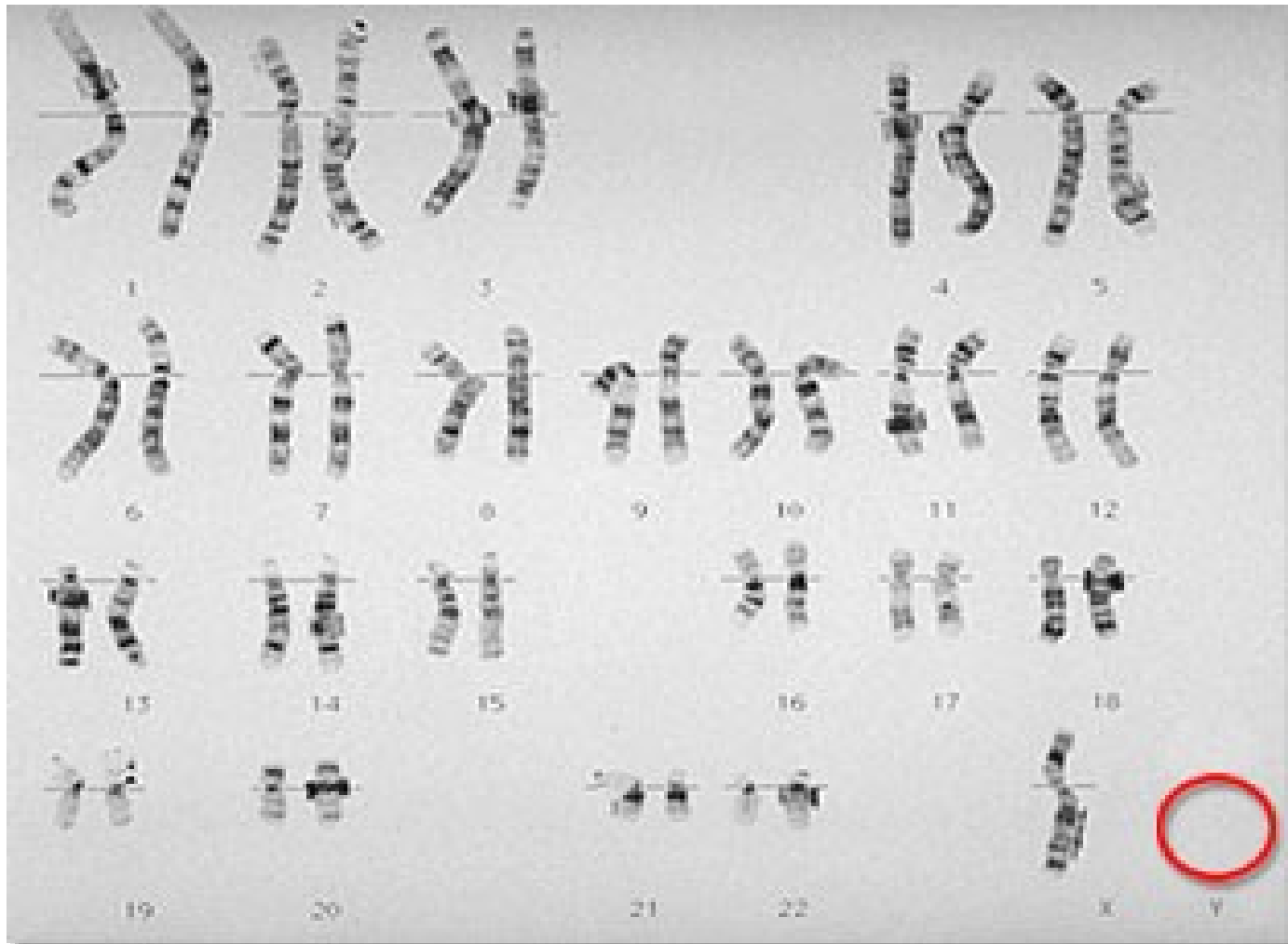


www.angelfire.com/wy/XXY/

Sindrome di Klinefelter (XXY)

- Many people with this disorder have no idea they have it until they hit puberty or try to have children.
- At puberty, men with this syndrome often develop ***more breast tissue than normal***, have a ***less muscular body***, and grow ***very little facial or body hair***.
- When men with Klinefelter syndrome try to have children, most discover that ***they are sterile*** because they cannot produce sperm.
- ***Learning disabilities*** (not categorized as mental retardation) are also a common problem for them.

Sindrome di Turner (X0)

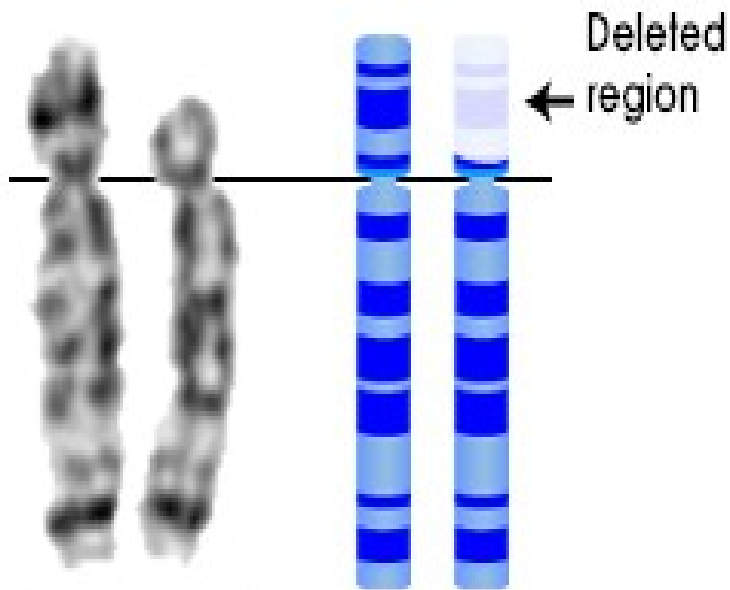


Sindrome di Turner

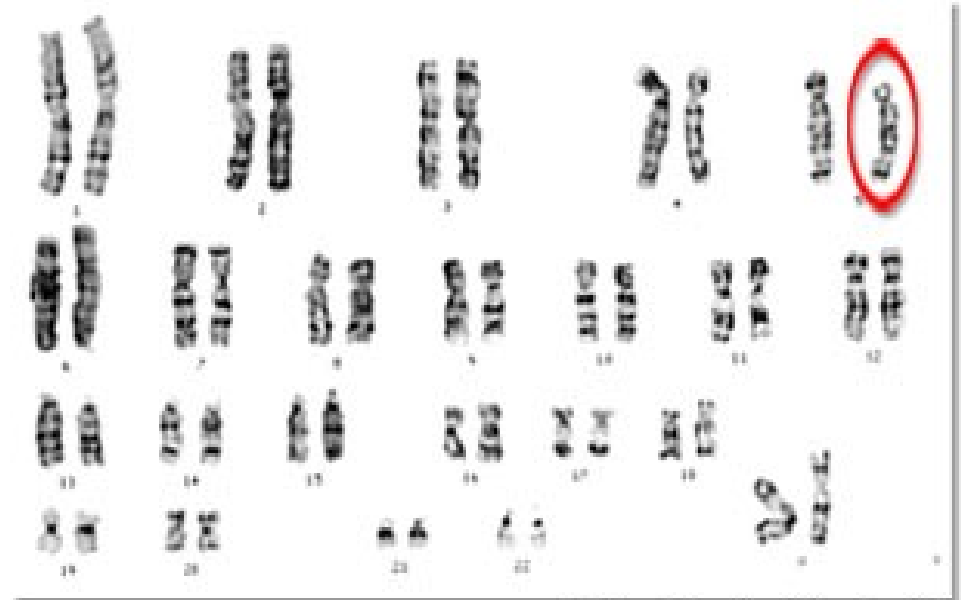
- It affects ***1/2000*** to ***1/2500 babies***.
- Turner syndrome ***affects growth and sexual development***.
- Girls with this disorder are ***shorter than normal***, and may ***fail to start puberty*** when they should. This is because ***the ovaries fail to develop properly***.
- Women with Turner syndrome appear to have a ***stocky appearance***, arms that turn out slightly at the elbow, a ***receding lower jaw***, a ***short webbed neck***.
- Other medical symptoms include: ***lymphedema*** (swelling of hands and feet), ***heart and/or kidney defects***, high blood pressure, and ***infertility***.



Sindrome del “Cri du Chat”

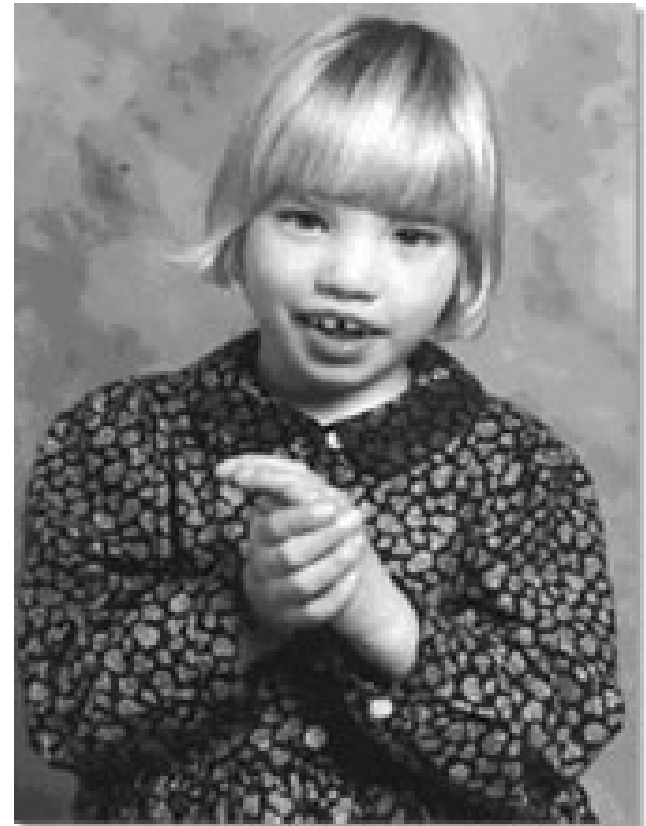


Cri-du-chat Chromosome 5 pair



Sindrome del “Cri du Chat”

- It affects between ***1/20,000*** and ***1/50,000*** babies.
- Babies are usually ***small at birth***, and may ***have respiratory problems***.
- Often, ***the larynx doesn't develop correctly***, which causes the signature cat-like cry.
- People who have cri-du-chat have a ***small head*** (microcephaly), an ***unusually round face***, a ***small chin***, ***widely set eyes***, folds of skin over their eyes, and a small bridge of the nose.

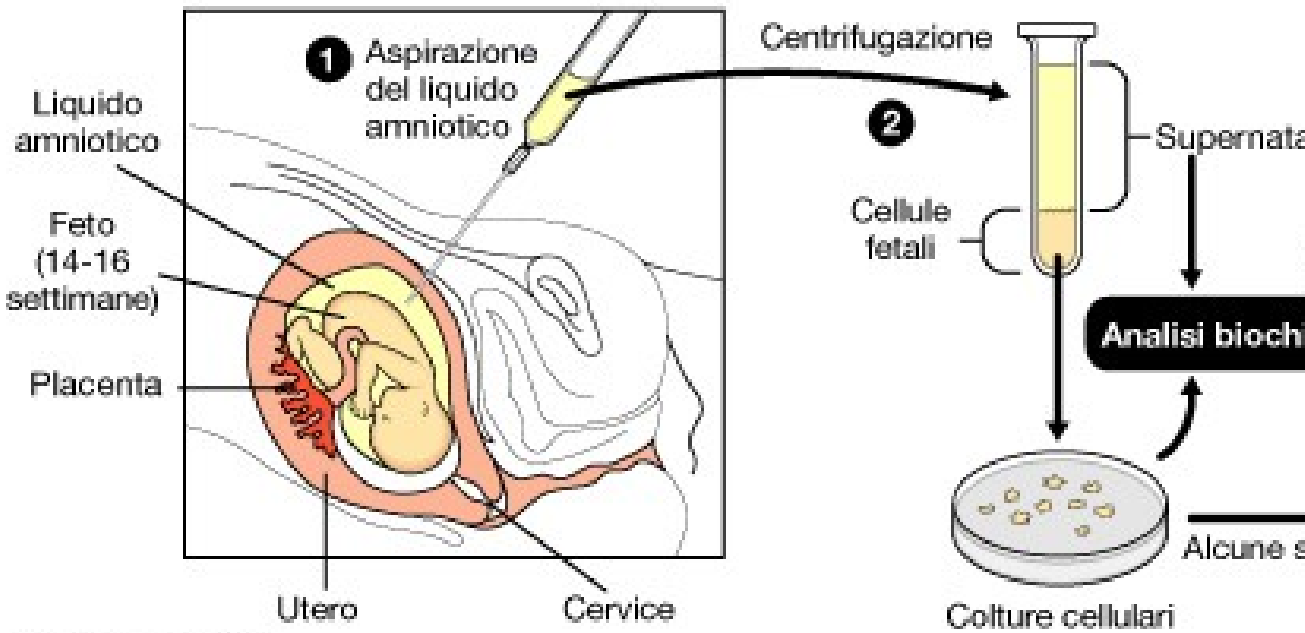


CdC Support Group
www.cridchat.u-net.com

Sindrome del “Cri du Chat”

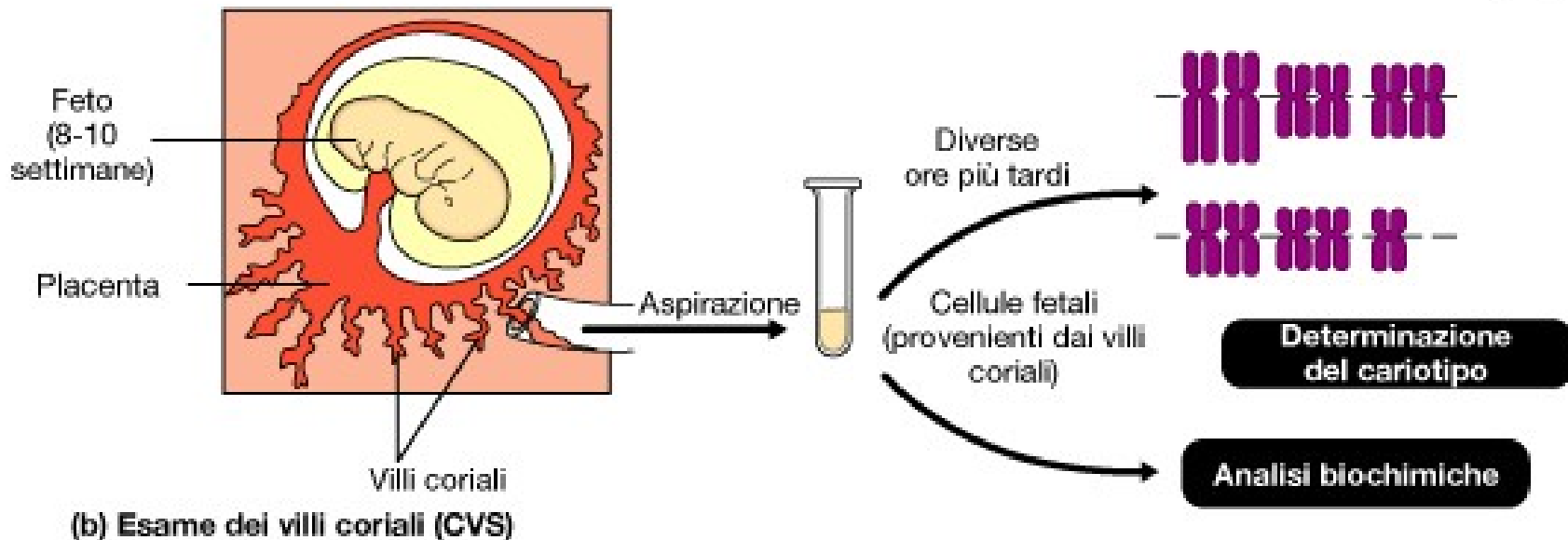
- Several problems occur inside the body, as well.
- A small number of children have ***heart defects, muscular or skeletal problems, hearing or sight problems.***
- As they grow, people with “cri-du-chat” usually have ***difficulty walking and talking correctly.***
- They may have ***behavior problems*** (such as hyperactivity or aggression), and ***severe mental retardation.***
- Unfortunately, most people with this disorder don't survive to adulthood.

La diagnosi precoce di anomalie cromosomiche nel feto è possibile a partire dalla 10^a settimana di gravidanza



(a) Amniocentesi

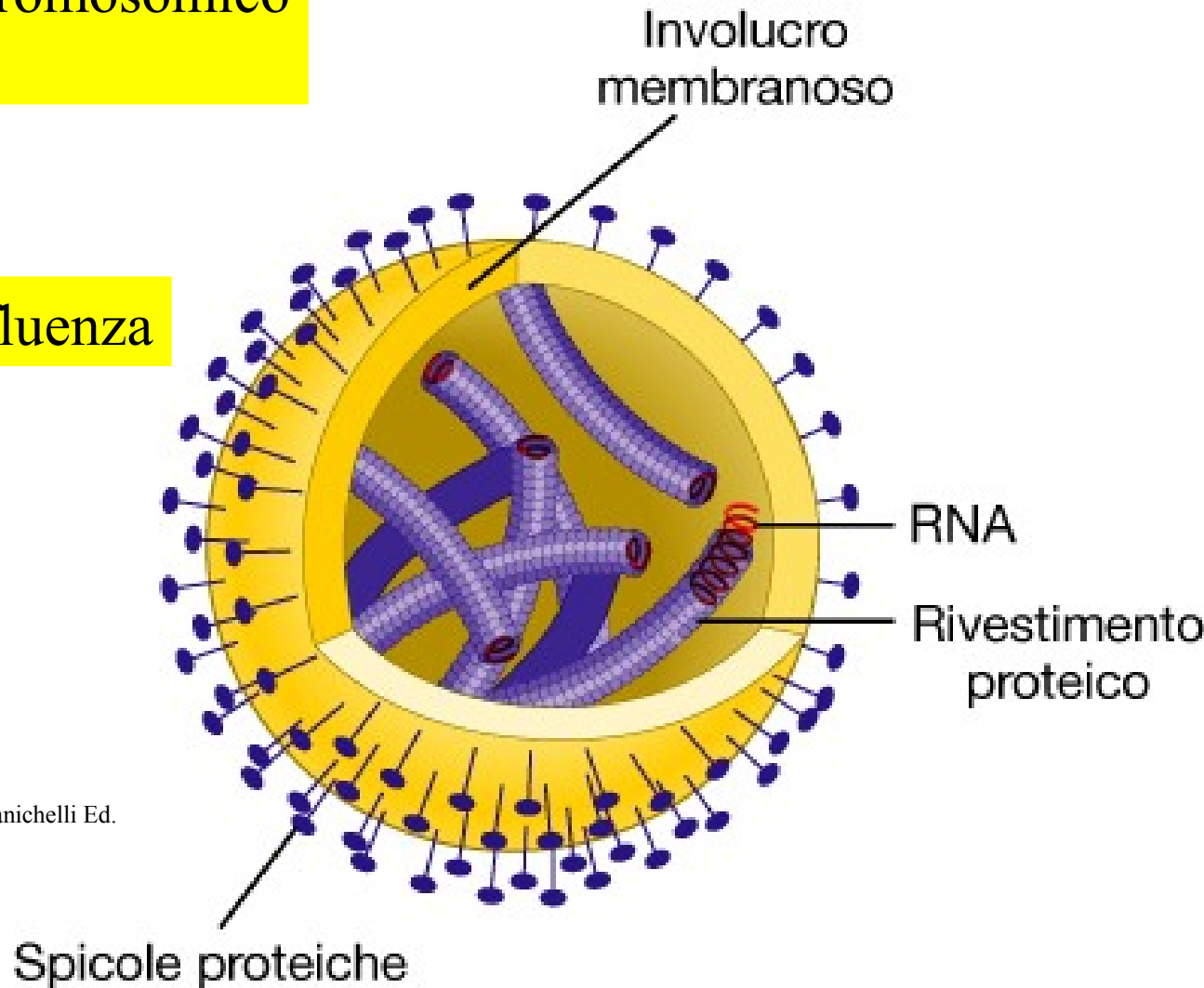
4 Determinazione del cariotipo



(b) Esame dei villi coriali (CVS)

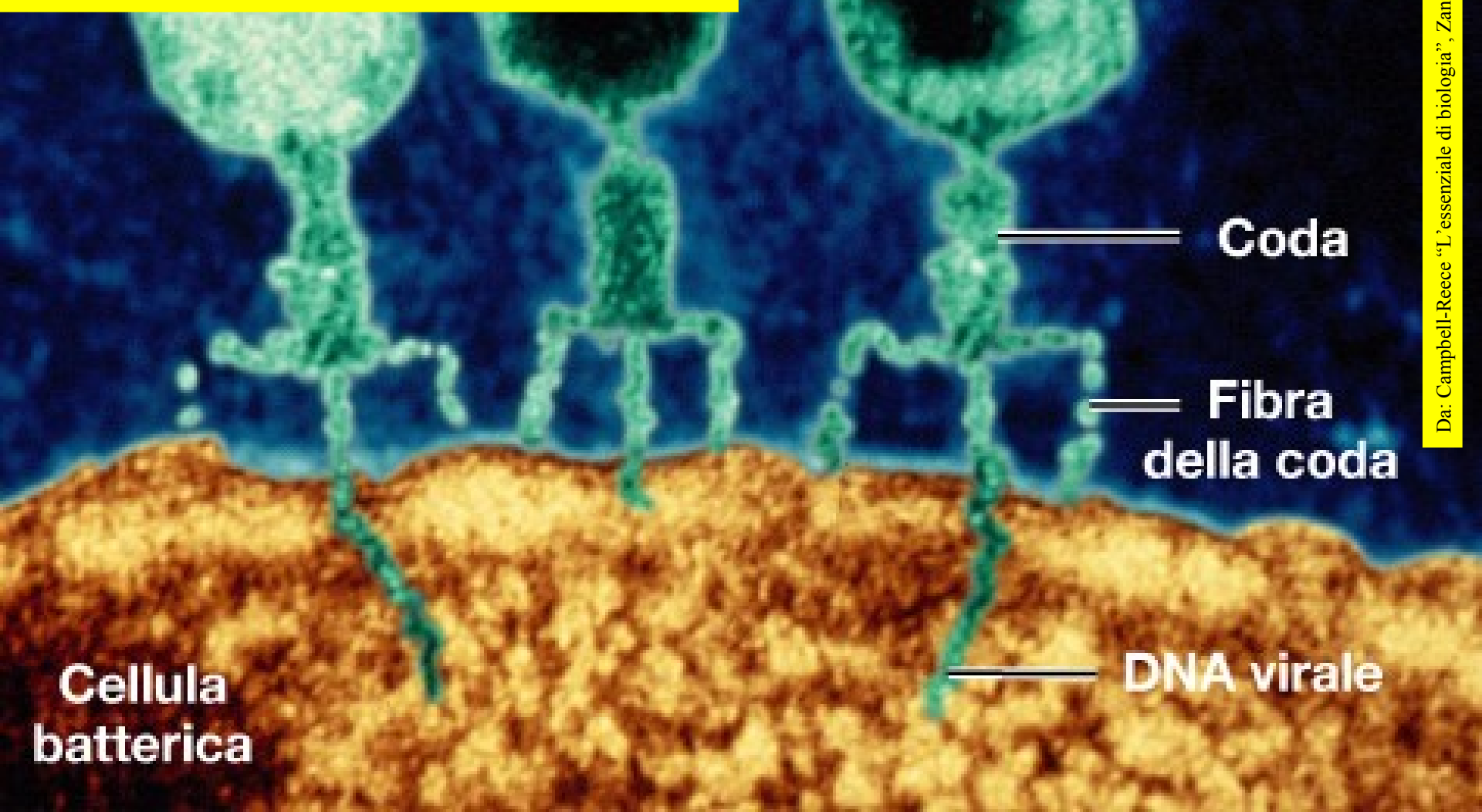
Altre fonti note di mutazioni sono rappresentate da *inserzioni, naturali o artificiali*, di DNA esogeno nel corredo cromosomico di un individuo

Il virus dell'influenza



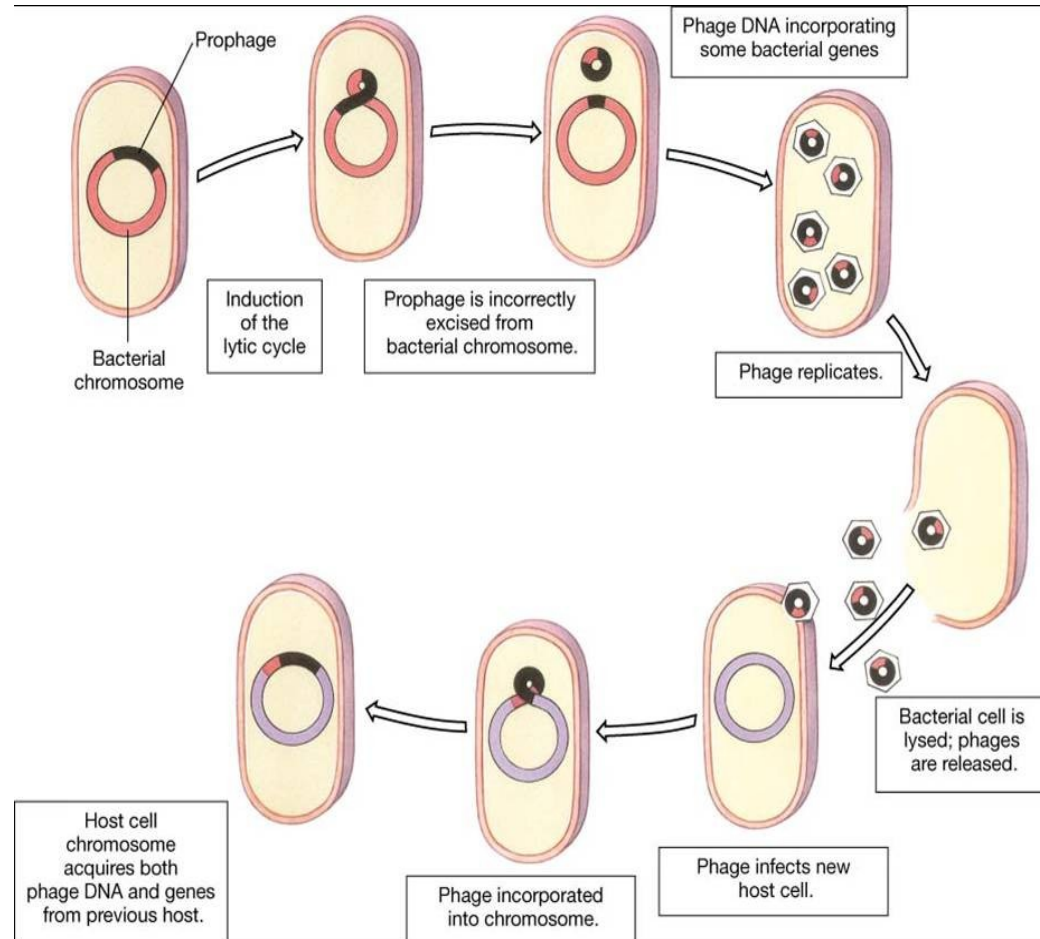
Da: Campbell-Reece "L'essenziale di biologia", Zanichelli Ed.

I virus sono aggregati altamente organizzati di DNA o RNA, proteine e lipidi, capaci di replicarsi solo all'interno di cellule batteriche o eucariotiche



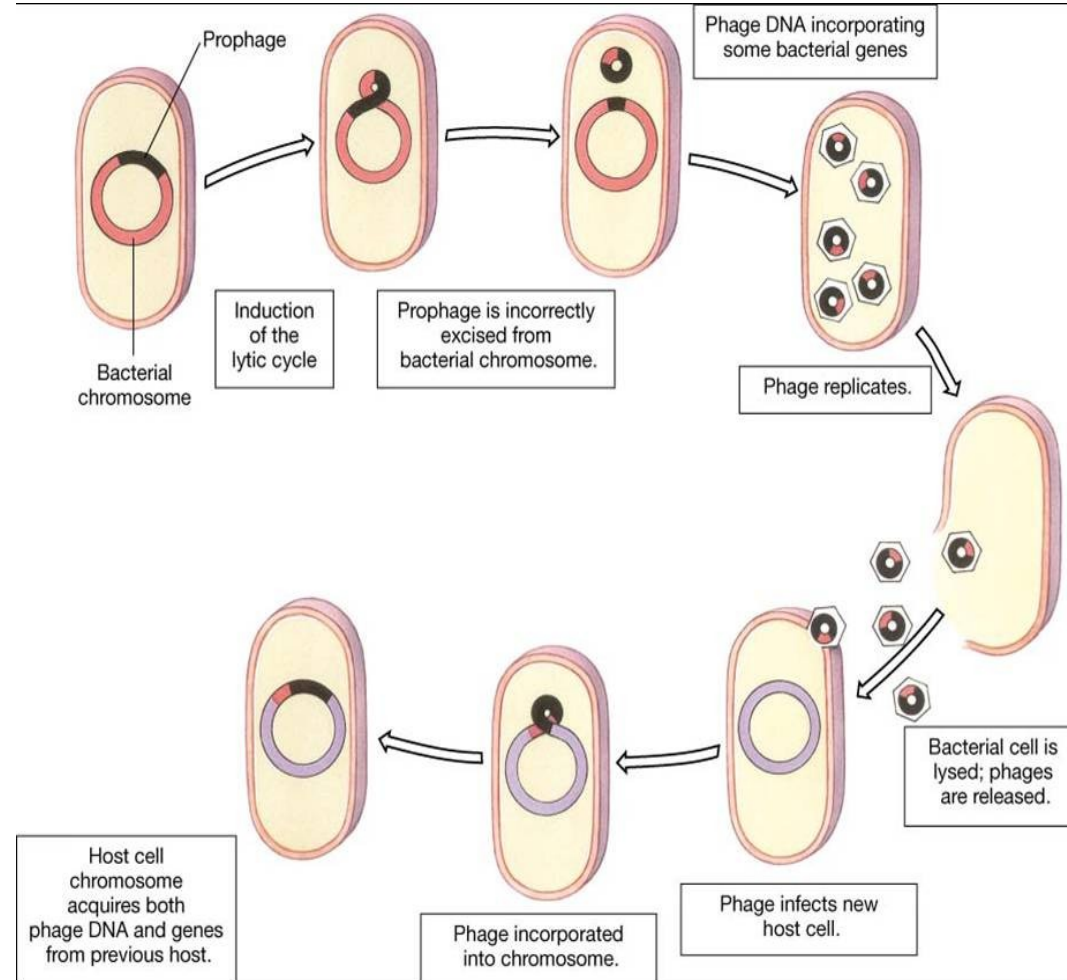
Trasduzione

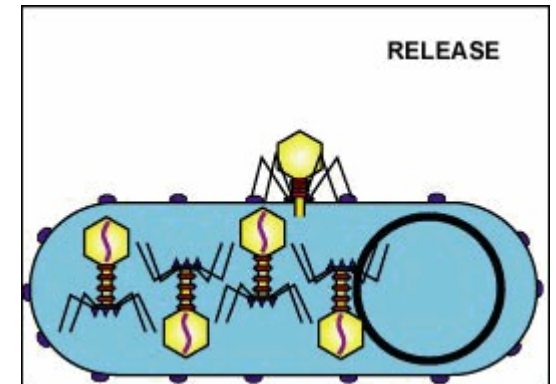
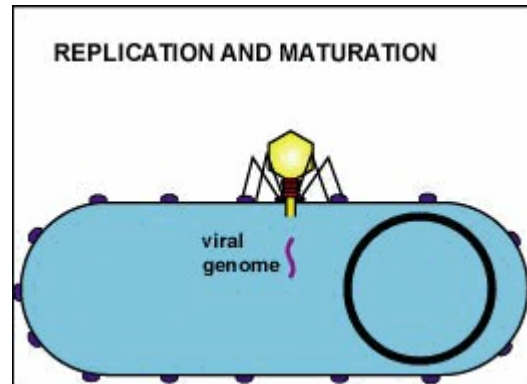
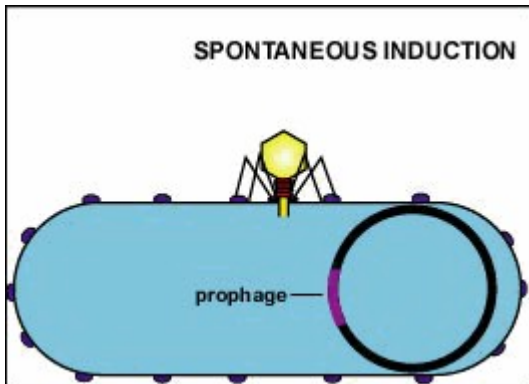
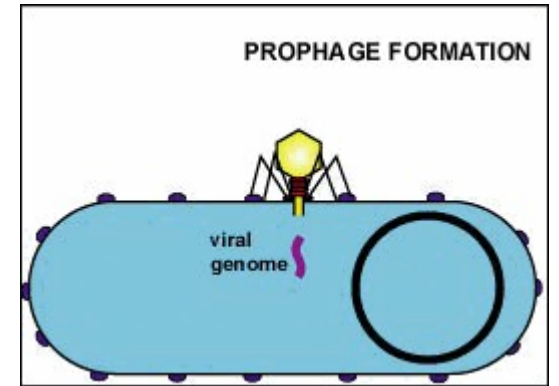
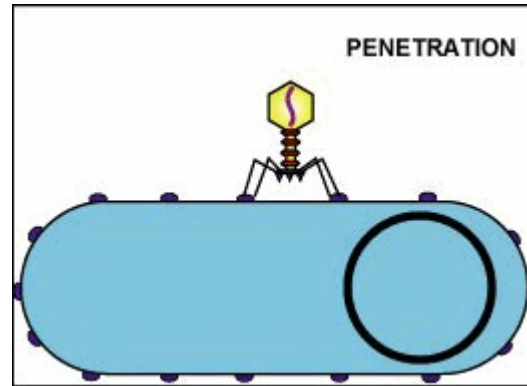
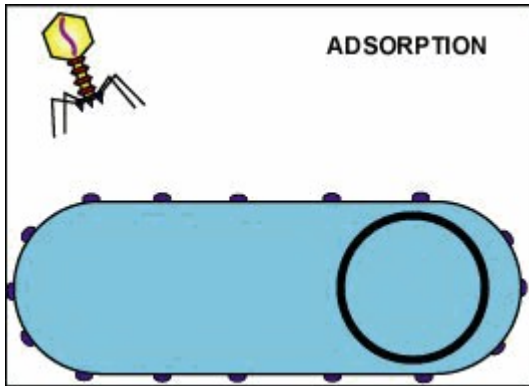
- Alcuni virus operano un ciclo lisogeno. Dopo che **il materiale genetico virale** entra nella cellula, **viene integrato nel cromosoma batterico**.
- I batteri “figli”, generati nella duplicazione, avranno lo stesso genoma della cellula madre, per cui anche la porzione genetica virale.
- A un certo punto, il genoma virale può ciclizzarsi e dare origine a un ciclo litico.
- Nella scissione del DNA virale dal DNA batterico, si potrebbero verificare diversi errori, con la possibilità che interi geni o porzioni di geni vengano ciclizzati insieme al genoma virale, dando origine a virus che contengono geni batterici.
- Il cromosoma virale integrato col genoma batterico viene **chiamato profago**.



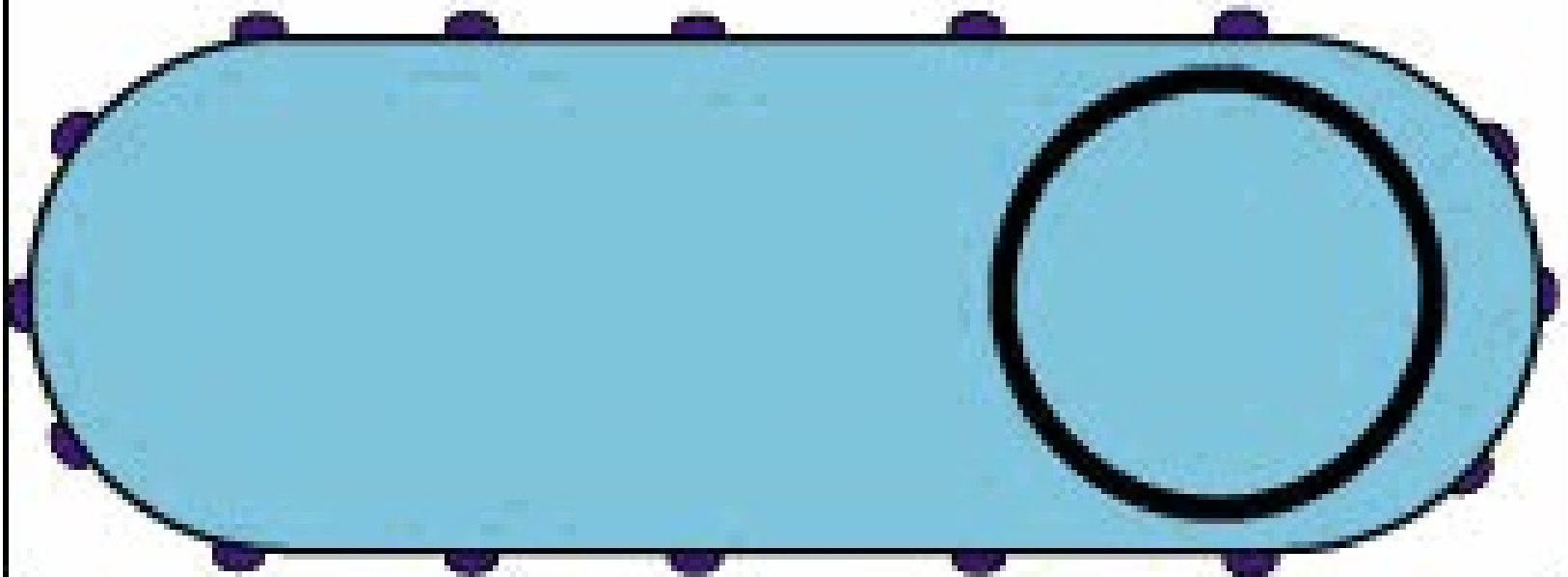
Trasduzione

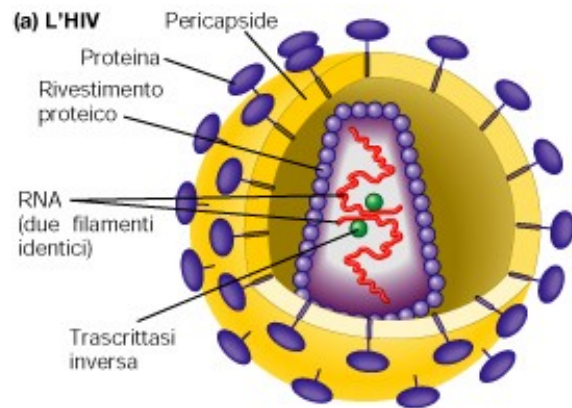
- ***Quando il profago viene inserito in una nuova cellula***, dove si realizzerà il ciclo lisogeno, sarà inglobato nel cromosoma batterico e i geni presenti nel profago potrebbero ***conferire nuove caratteristiche alla cellula infettata***.
- Il DNA batterico, quando sarà inserito nella cellula ricevente potrebbe:
 - essere integrato nel genoma dell'ospite, trasmettendo nuove caratteristiche del donatore
 - rimanere nel citoplasma senza replicarsi, ma capace di conferire nuovi caratteri fenotipici e metabolici all'ospite
 - diventare circolare e funzionare come un episoma



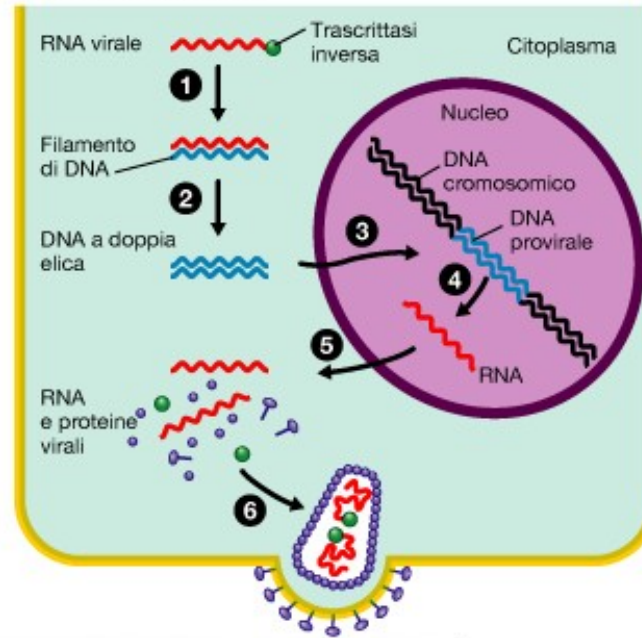


ADSORPTION

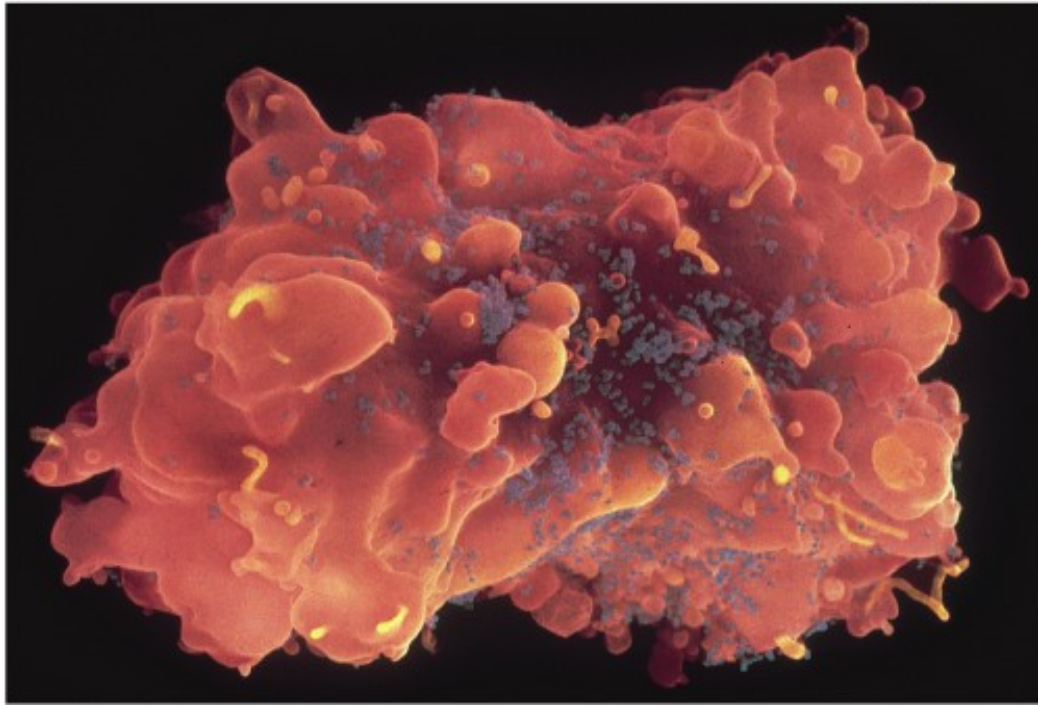




(b) Il comportamento dell'acido nucleico dell'HIV in un cellula infettata

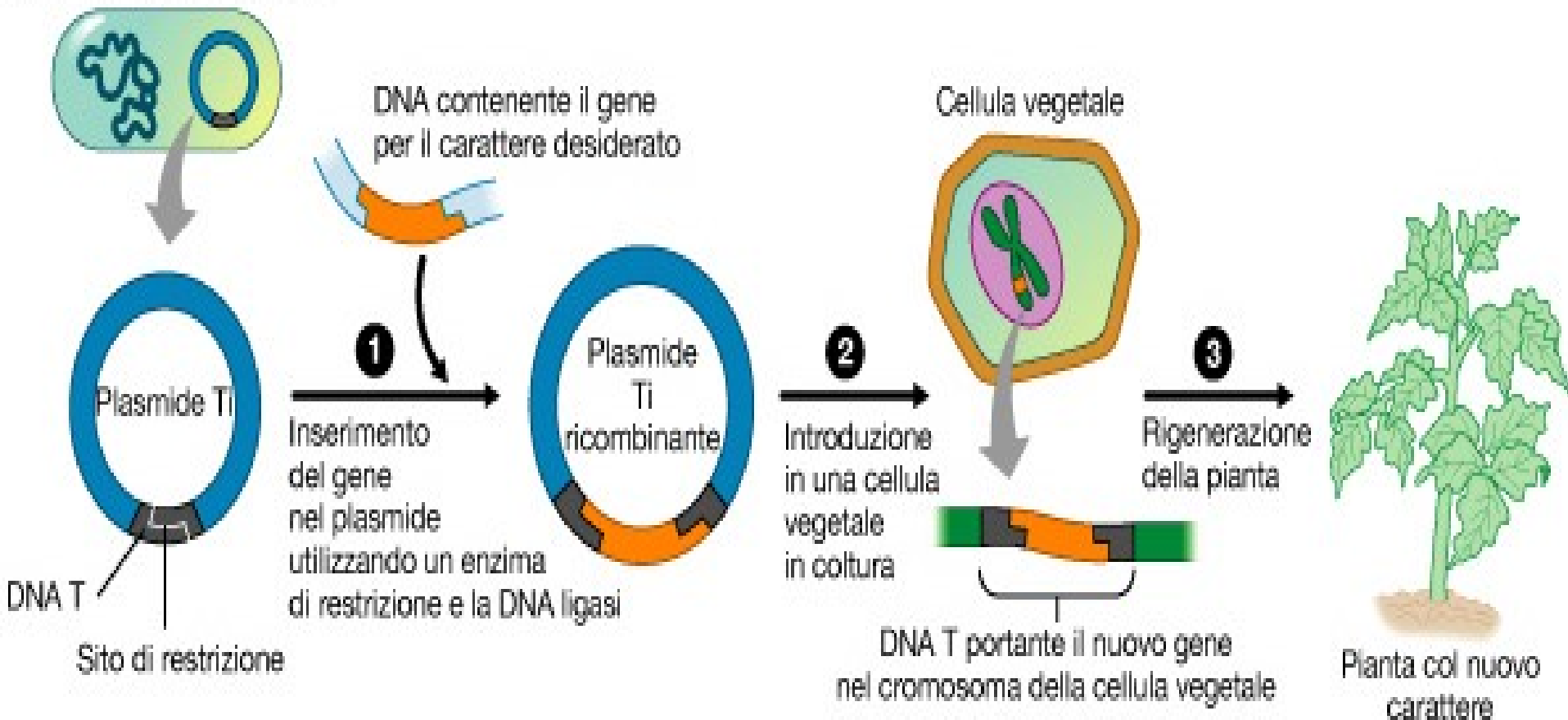


(c) L'HIV mentre sta infettando un leucocita



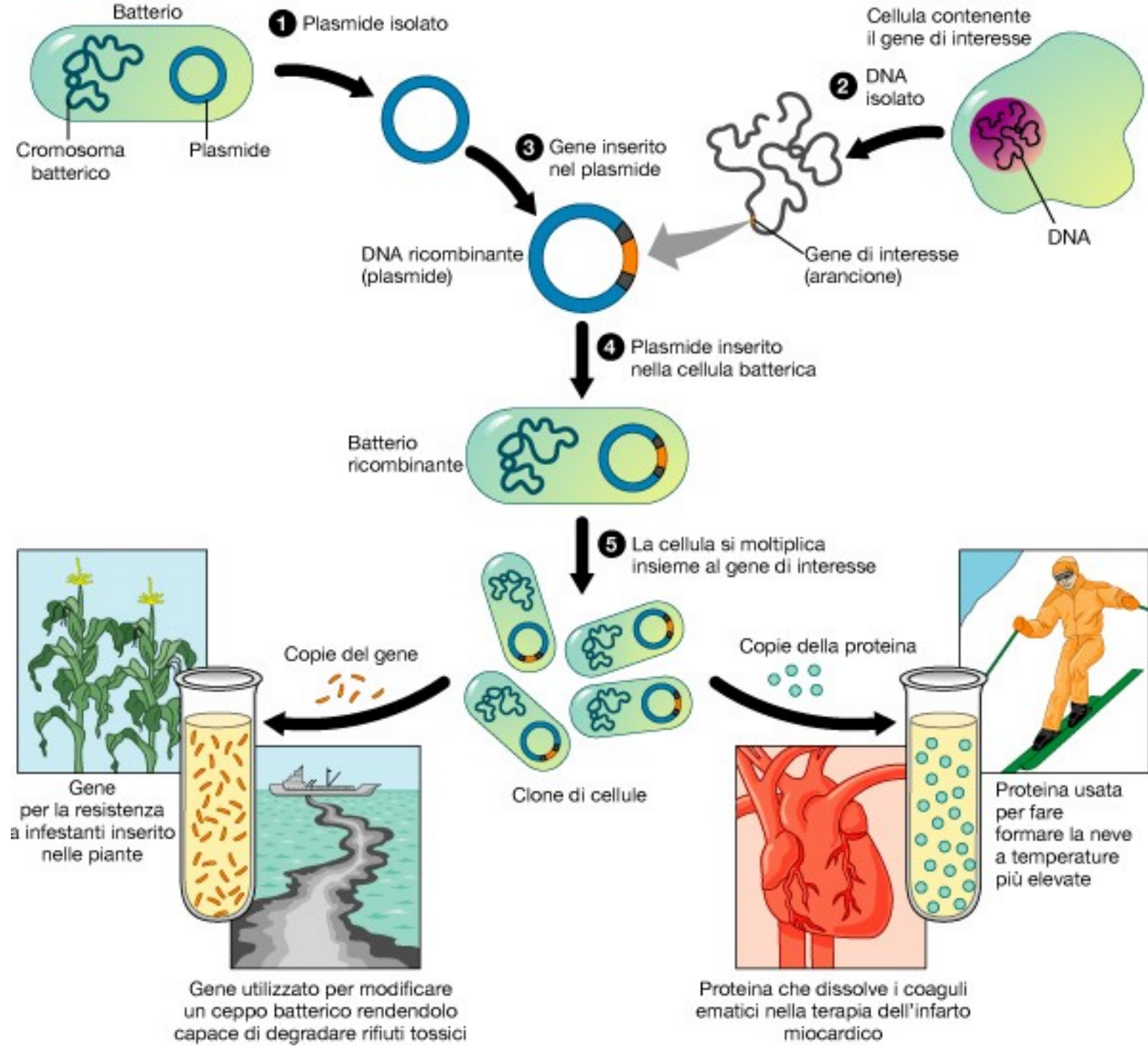
Al pari dei virus, anche l'uomo è oggi in grado di inserire materiale genetico selezionato nel corredo cromosomico normale di batteri, piante e animali, creando *organismi geneticamente modificati (OGM)*

Agrobacterium tumefaciens





Una coltivazione di mais transgenico “BT-11”, resistente agli insetti



E per concludere:

- L'evoluzione, il processo di variazione ereditaria che si svolge nelle specie con il trascorrere del tempo, costituisce la base di interpretazione e unificazione di tutti i campi della biologia.
- Molto probabilmente ci sarà sempre un vivace dibattito scientifico sui meccanismi dell'evoluzione, naturale o artificiale, ma ormai non ci si chiede più se gli organismi si evolvano.