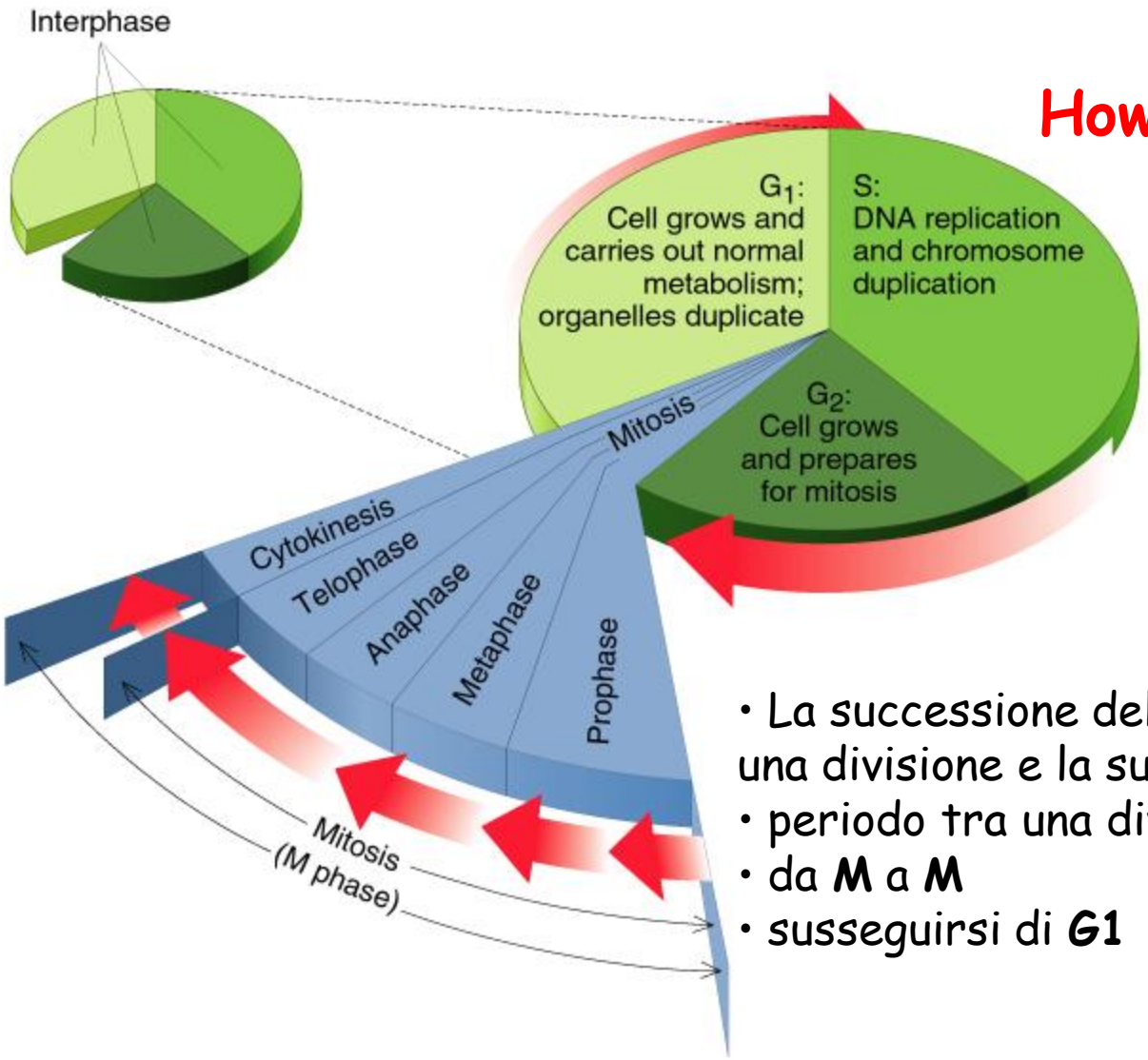
Lezione 4

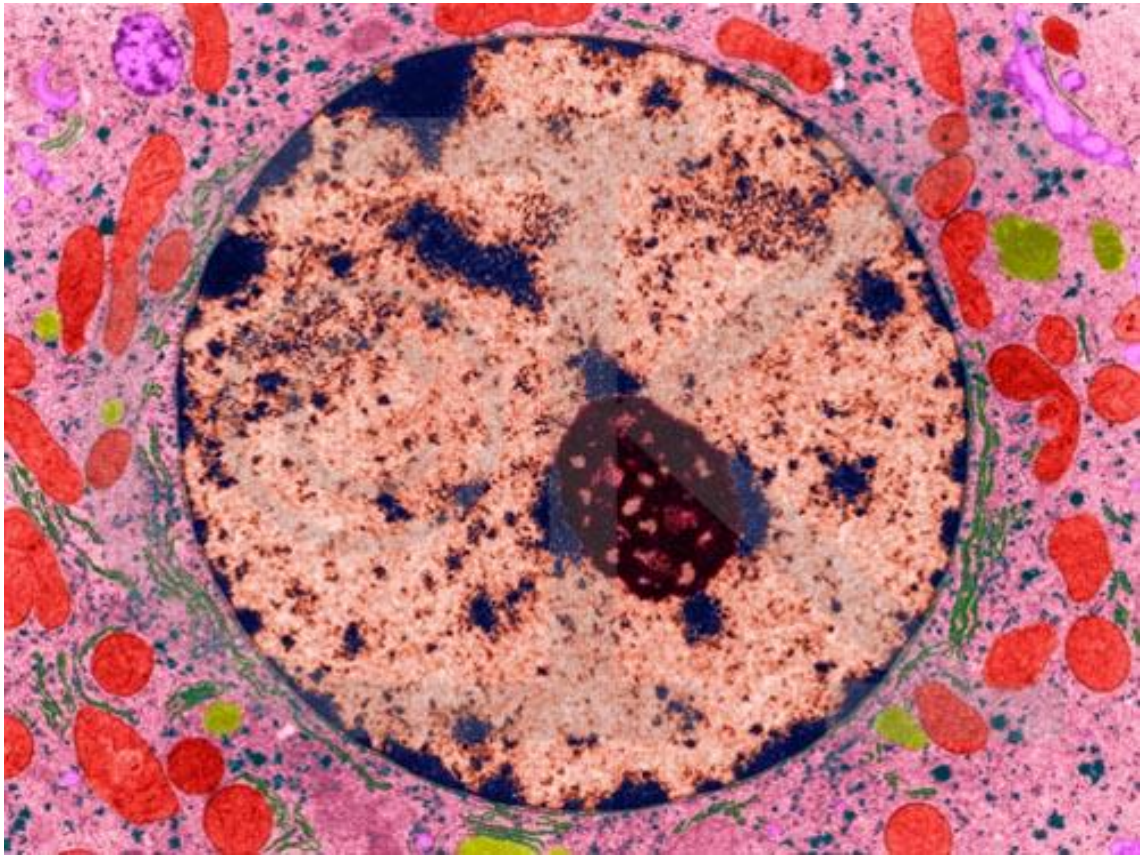
Ciclo cellulare



Howard e Pelc, 1953

- La successione delle fasi della cellula tra una divisione e la successiva
- periodo tra una divisione cellulare e l'altra
- da **M** a **M**
- susseguirsi di **G1 - S - G2 - M**

- **G1 - S - G2** → **interfase** → elevata attivita' metabolica
- I cromosomi non sono visibili → nel nucleo cromatina decondensata e nucleoli



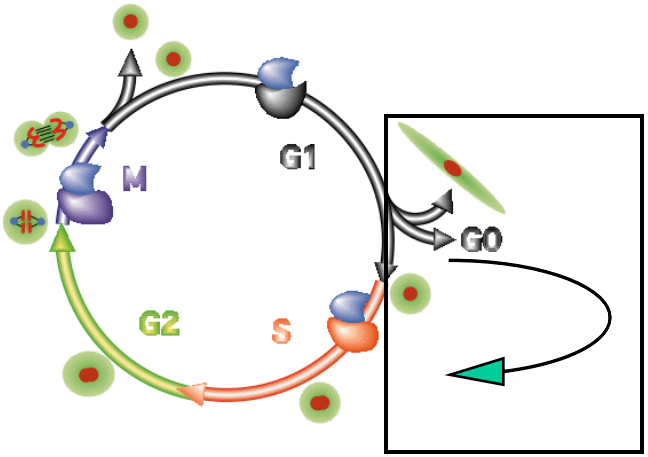
La variabilita' della durata dell'interfase dipende dalla durata della fase G1

La durata del ciclo cellulare in diversi tipi di cellule

SPECIE	INTERFASE (min)	MITOSI (min)
Physarum polycephalum	420	40
Pollo (fibroblasti)	700	23
Topo (fibroblasti)	1300	40
Criceto (fibroblasti)	640	24
Ratto (epitelio corneale)	14000	70

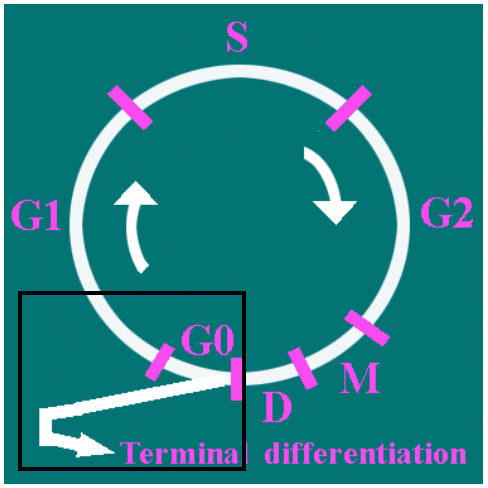
Cellule **ciclanti**

- Cellule ematopoietiche
- Spermatogoni



Cellule **transitoriamente quiescenti**

- osteoblasti (osso adulto)
- muscolari satelliti
- altre cellule staminali

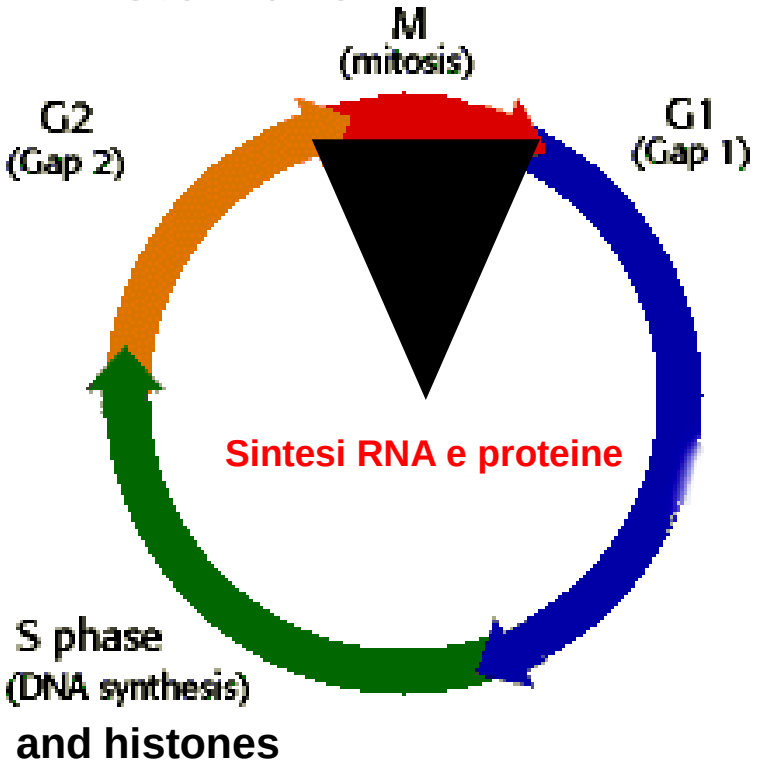


Cellule **irreversibilmente quiescent**

- cellule del Sertoli
- fibre muscolari
- granulociti
- neuroni

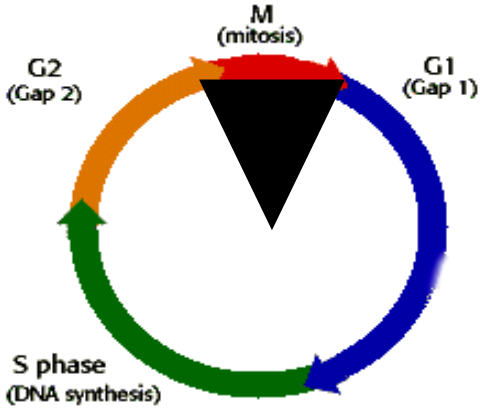
G1 - G2 → - sintesi di RNA
- proteine (fattori di regolazione)
- proteine istoniche (10%)

S → - sintesi del DNA
- sintesi 90% proteine istoniche



Il livello di trascrizione degli mRNA e di sintesi delle proteine e' relativamente costante durante il ciclo cellulare, cessa solo durante la fase M.
Solo gli istoni sono sintetizzati prevalentemente durante la fase S

LA MITOSI



E' il processo che porta alla equa ripartizione del corredo cromosomico e citoplasmatico nelle due cellule figlie

La mitosi segue il periodo di interfase durante il quale la cellula e' metabolicamente attiva e si prepara alla divisione

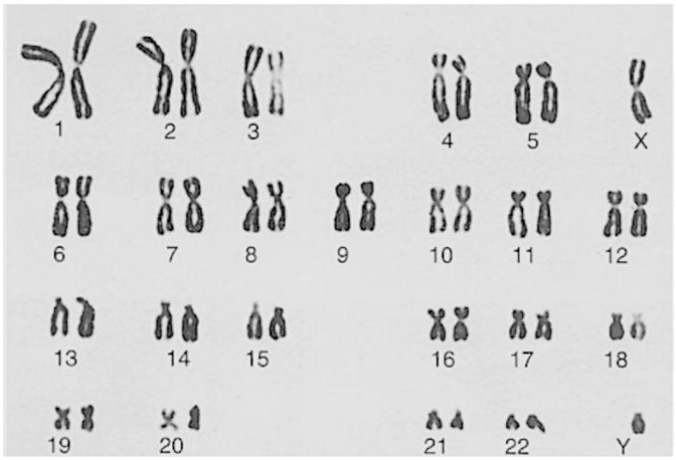
Fasi della mitosi:

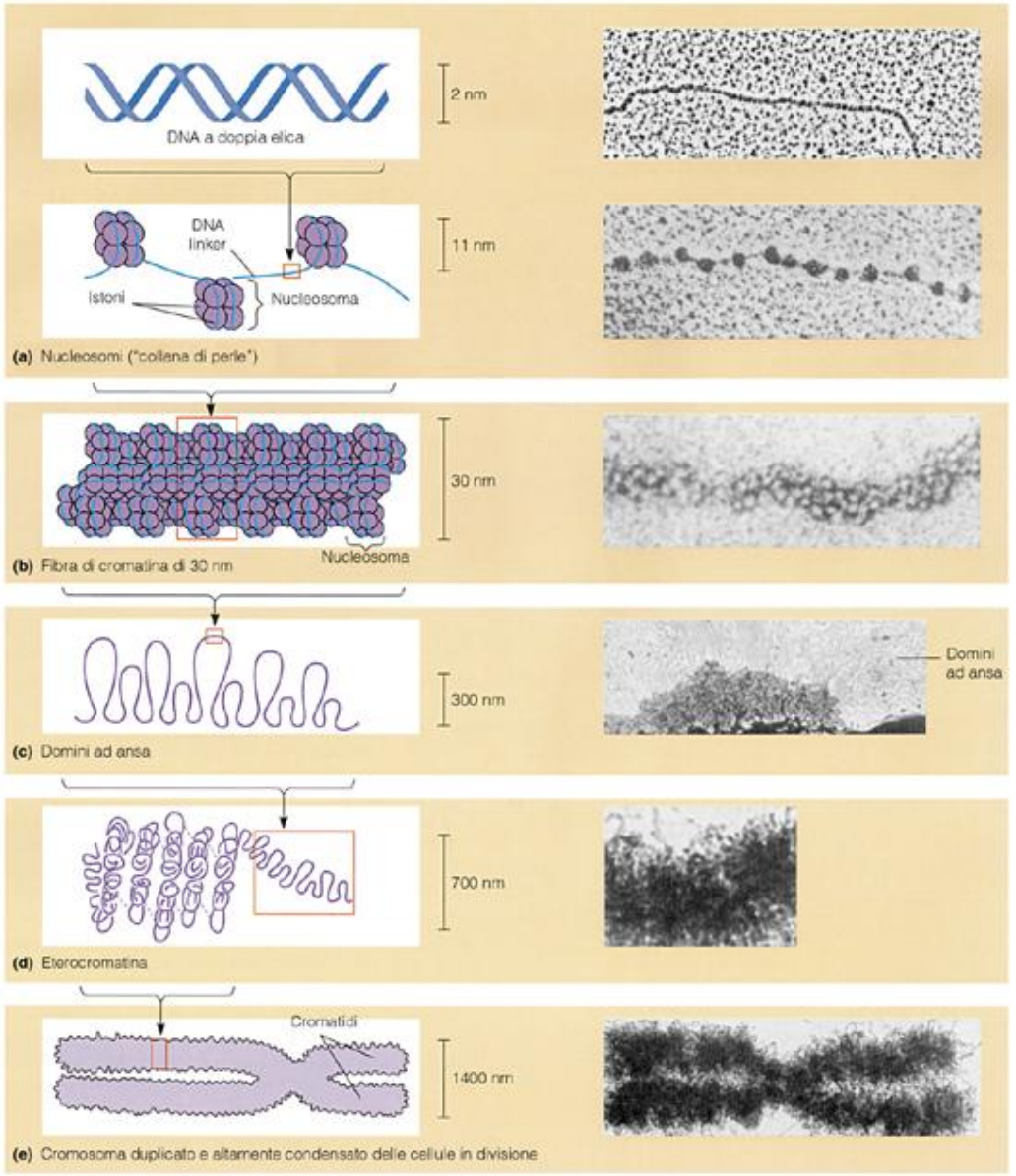
Profase
Prometafase
Metafase
Anafase
Telofase e citocinesi

Alla profase, la cromatina inizia un **processo di condensazione** che culminera' in metafase con la visualizzazione dei **cromosomi.**

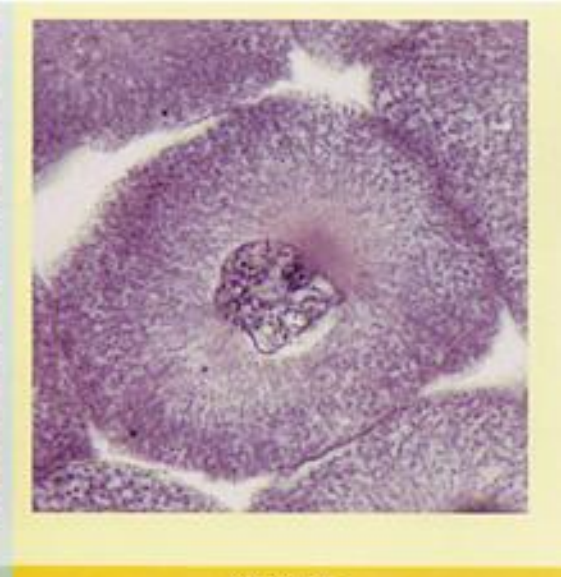
Dopo la duplicazione del DNA i **cromosomi sono formati da due cromatidi.**

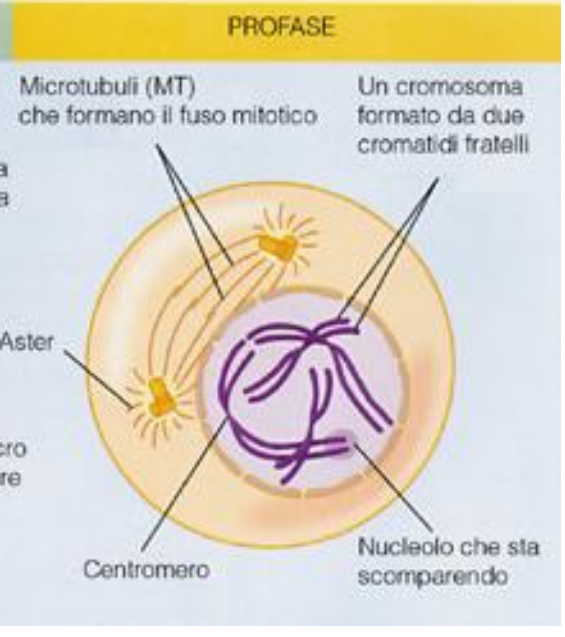
I cromosomi sono presenti in coppia, nell'uomo 2n=46

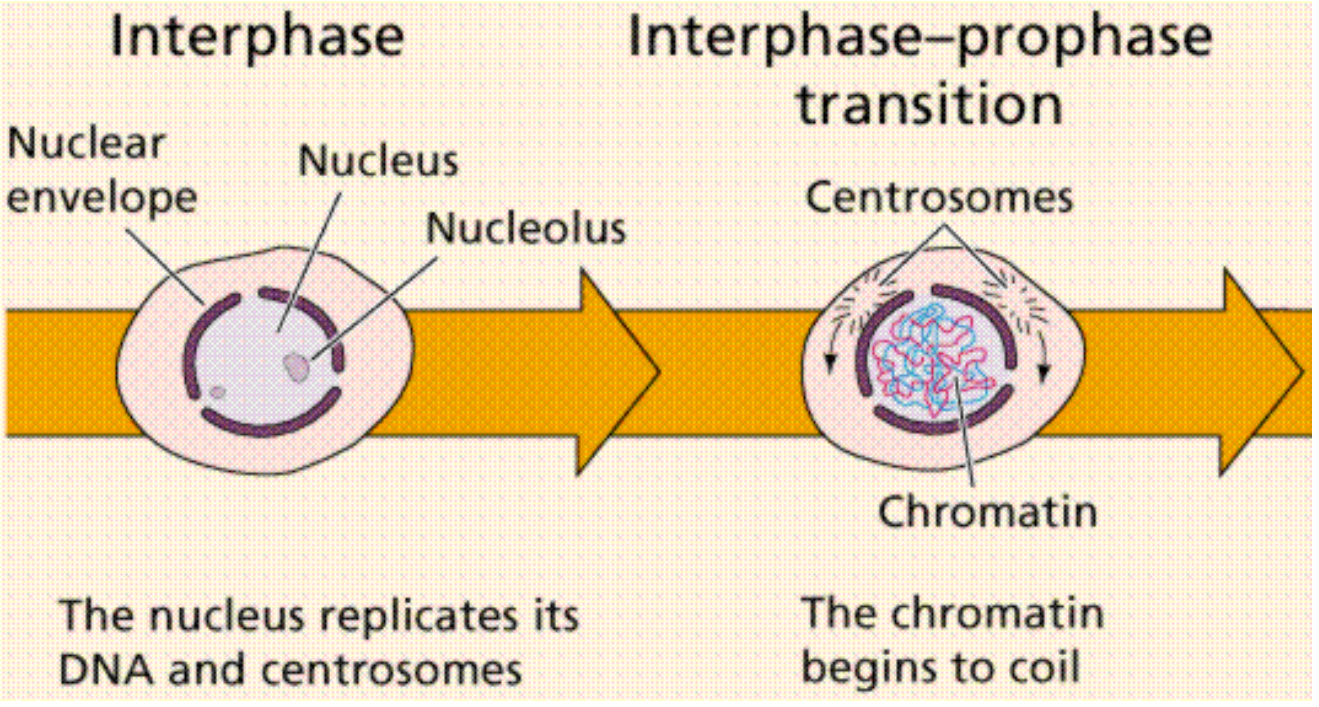




Profase

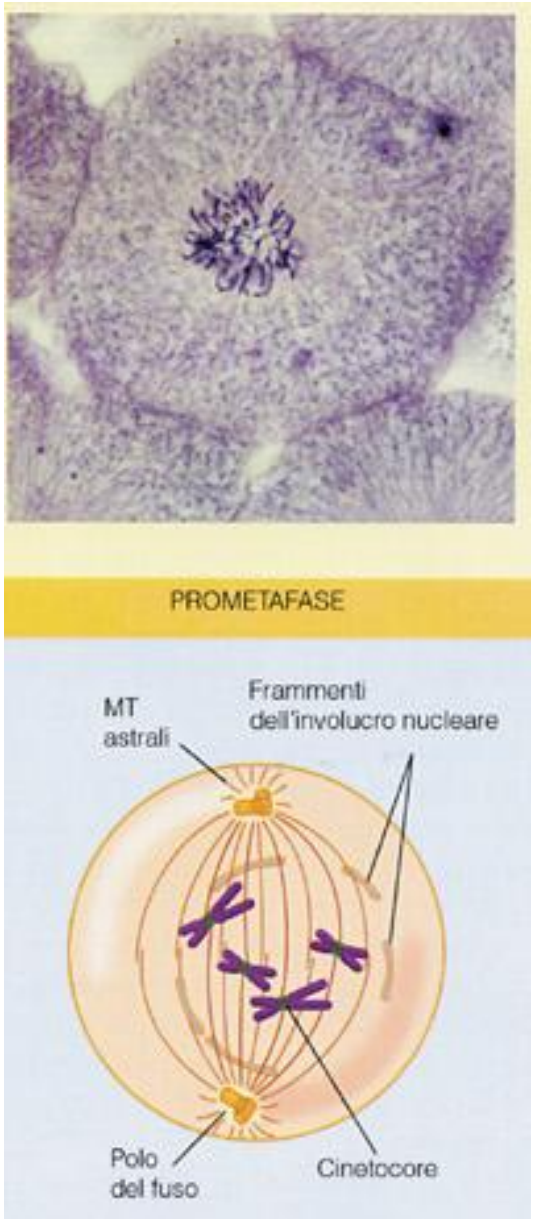


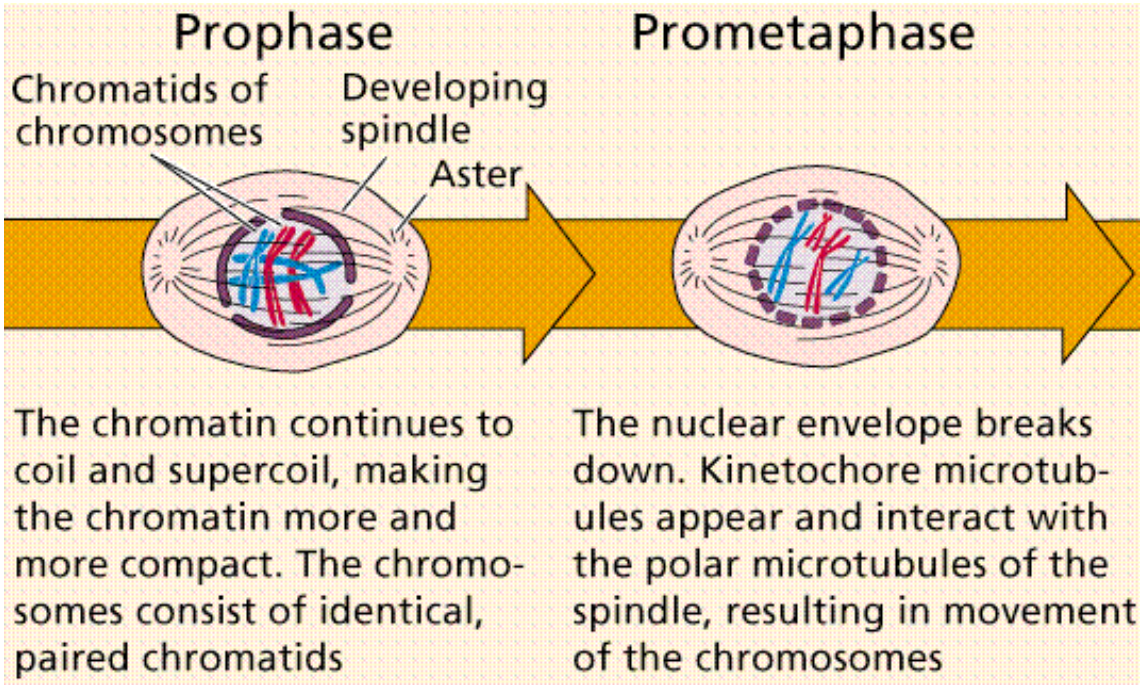




- la cromatina nel nucleo inizia a condensarsi e cominciano ad essere visibili i **cromosomi**
- il **nucleolo** scompare
- i **centrioli** cominciano a muoversi verso i poli opposti della cellula
- le **fibre del fuso** si estendono tra i due centrioli
- la **membrana nucleare** comincia a frammentarsi

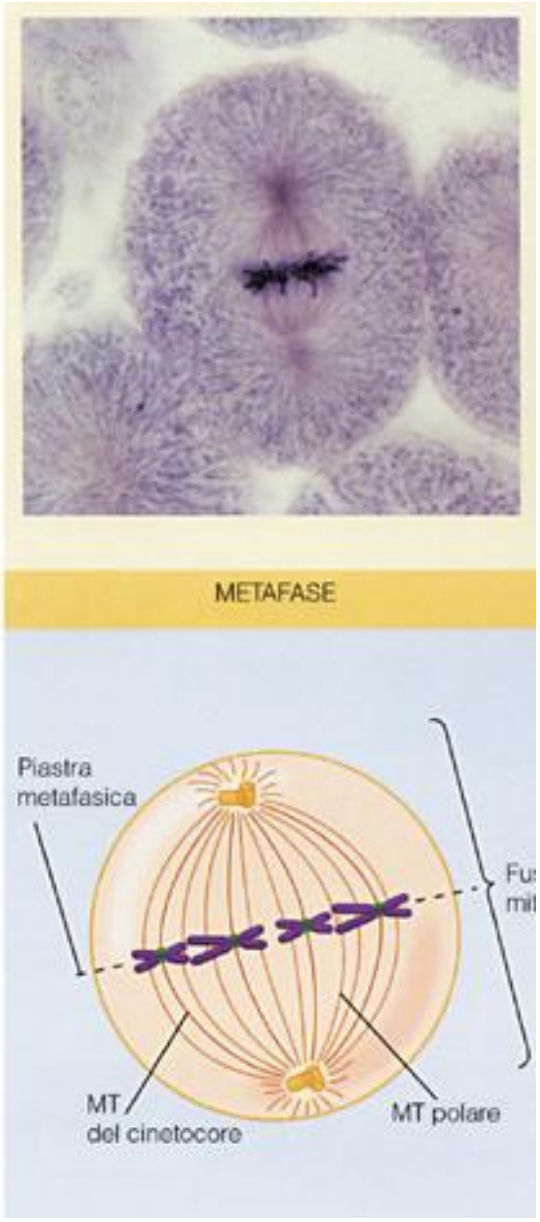
Prometafase

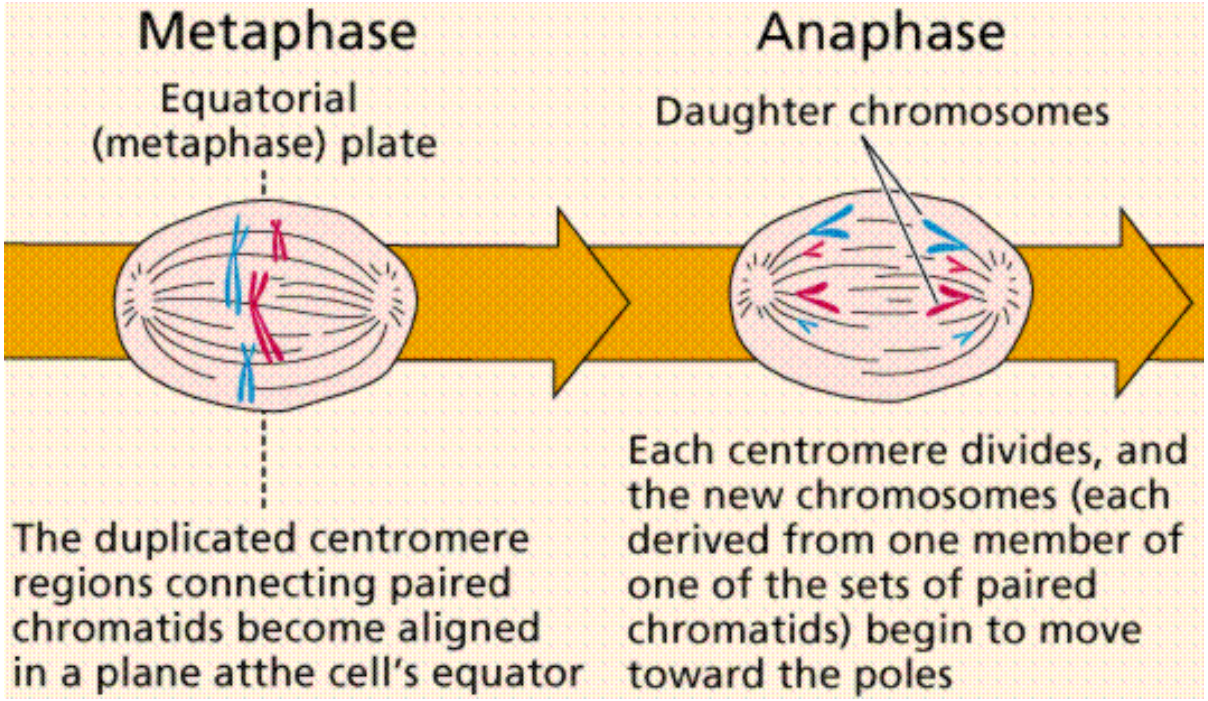




- la **membrana nucleare** si dissolve definendo l'inizio della prometafase
- Formazione del **cinetocore**
- I microtubuli si attaccano al cinetocore
- I cromosomi iniziano a muoversi

Metafase

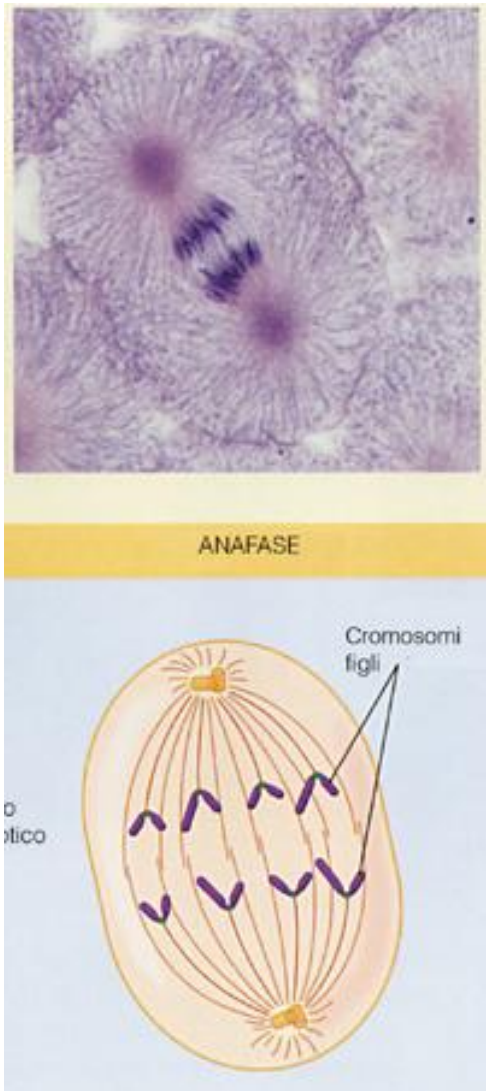


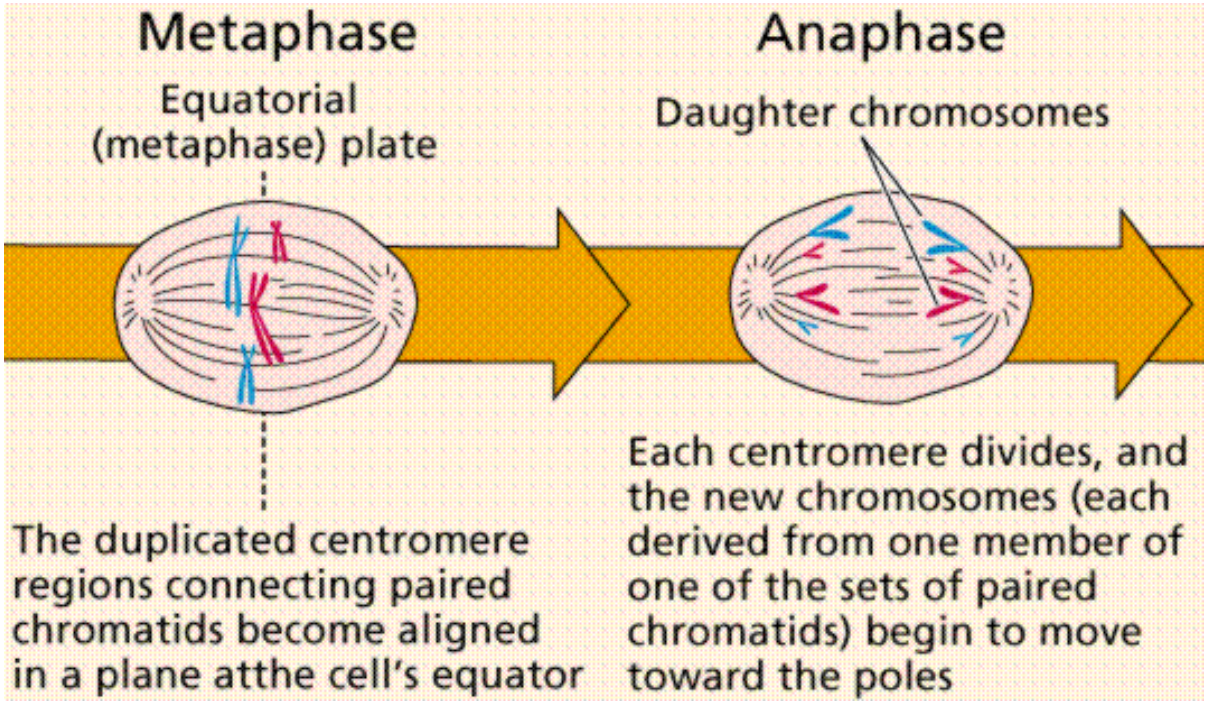


- Allineamento dei cromosomi sul piano equatoriale della cellula
- La disposizione della **piastra metafasica** assicura la corretta segregazione dei cromosomi

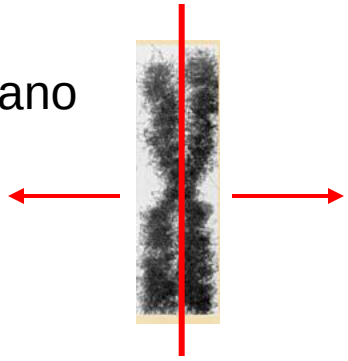
A questo stadio puo' essere effettuata l'analisi del cariotipo

Anafase





I cromatidi fratelli di ogni cromosoma si separano migrando verso i poli.



Anafase A: i microtubuli del cinetocore si accorciano trascinando i cromatidi verso i poli opposti

Anafase B: i poli del fuso si allontanano fra loro mentre i microtubuli polari si allungano

Le due fasi possono essere contemporanee

Alla profase, la cromatina inizia un **processo di condensazione** che culminera' in metafase con la visualizzazione dei **cromosomi.**

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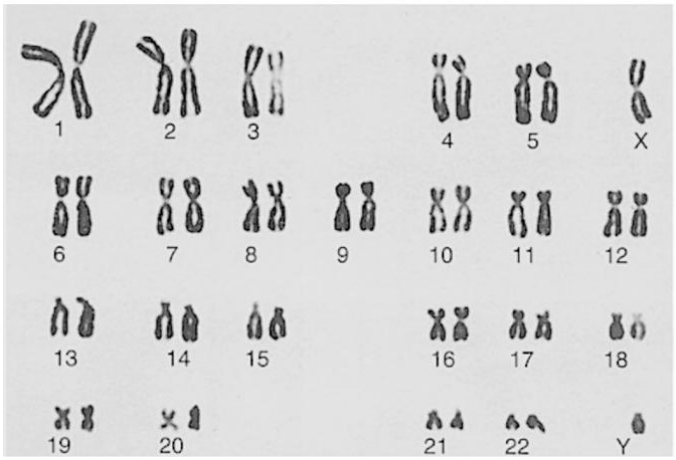
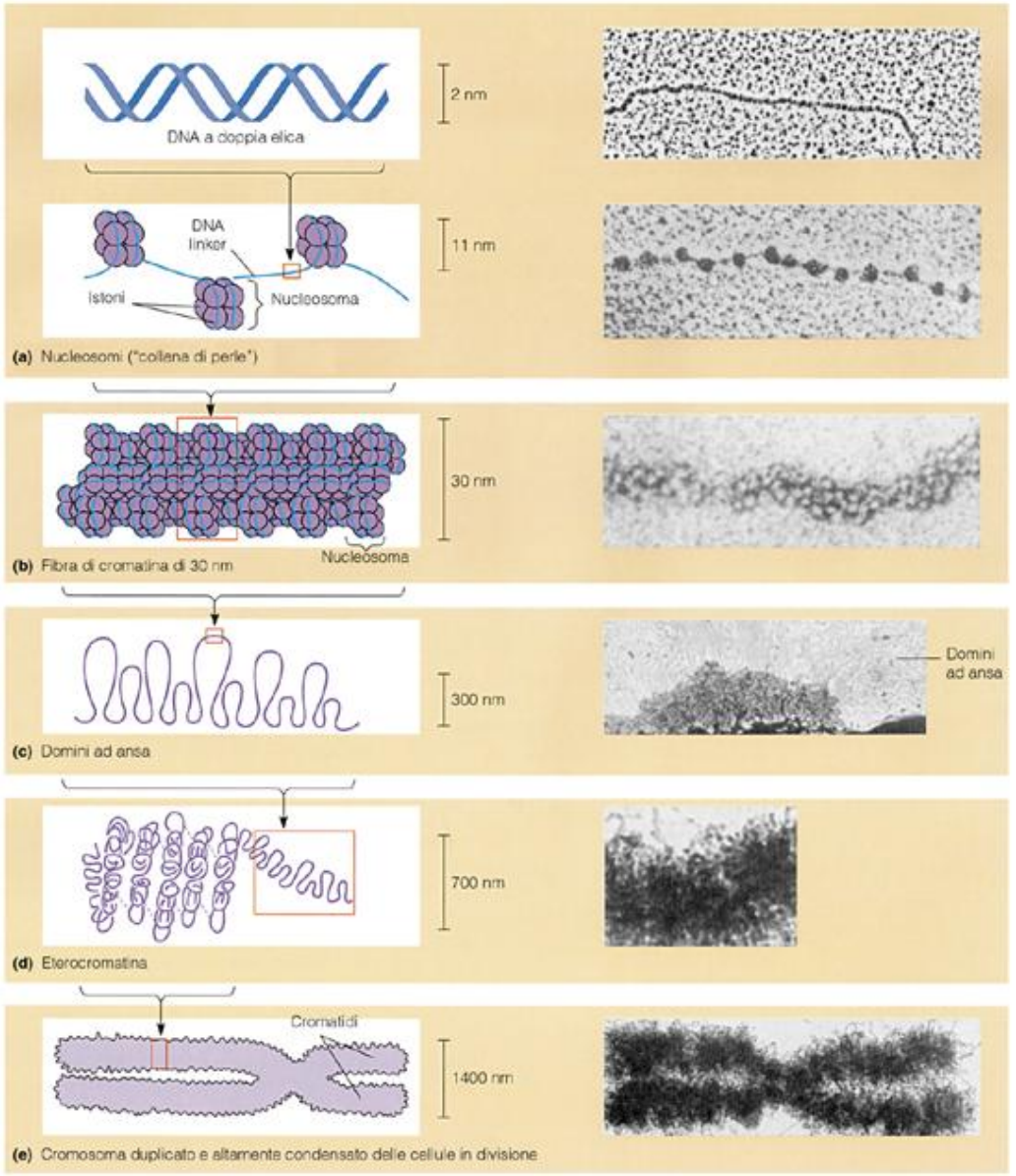
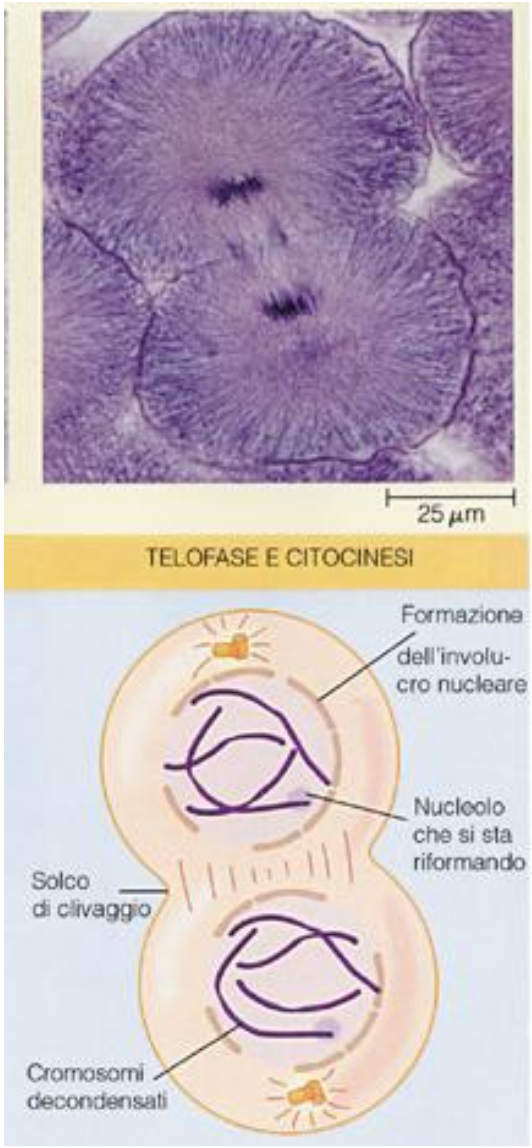
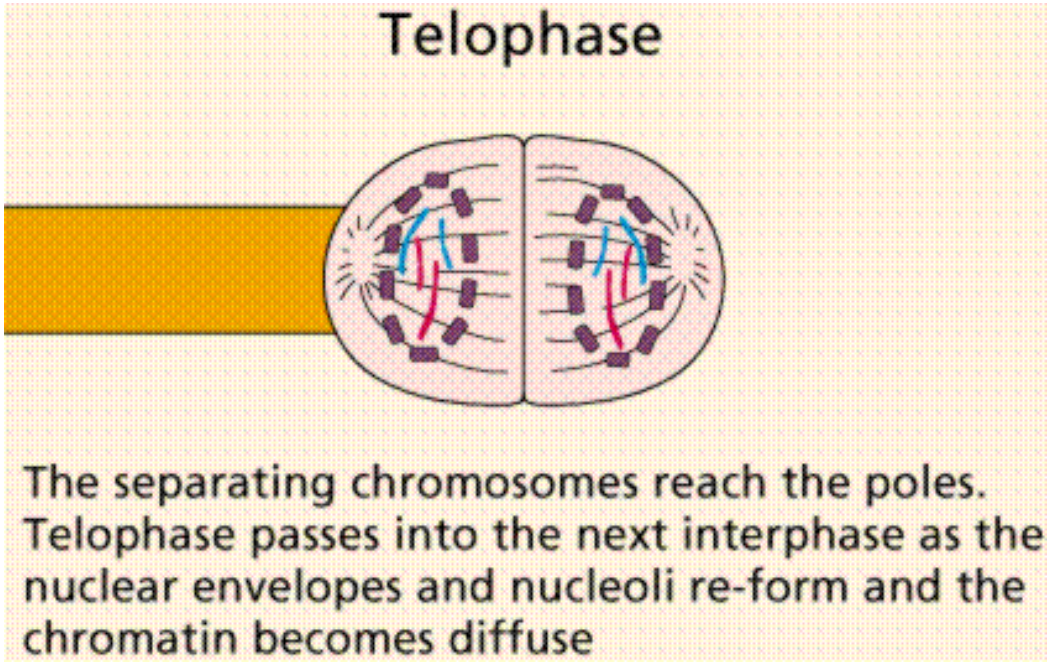




Telofase

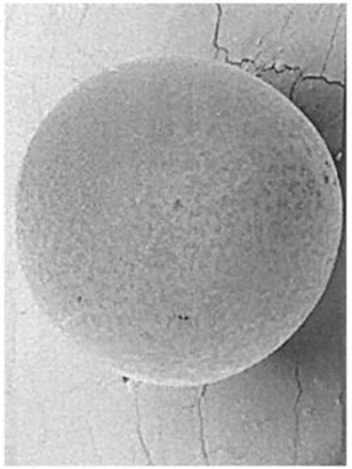


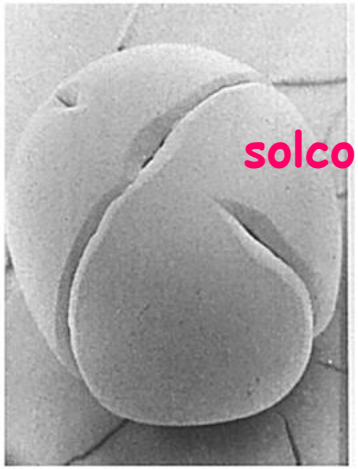


- I **cromatidi** arrivano ai poli opposti della cellula
- Si disgrega il fuso mitotico
- Nuove membrane si formano attorno ai nuclei
- I cromosomi iniziano a decondensarsi
- Si forma il nucleolo
- Ha inizio la **citodieresi o citocinesi**

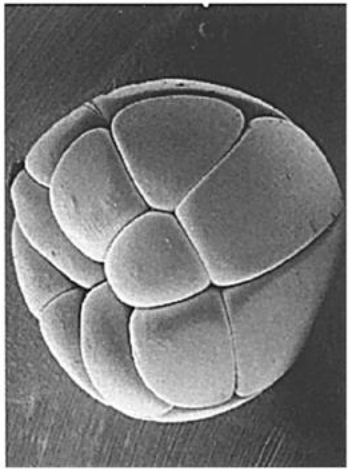
Citocinesi

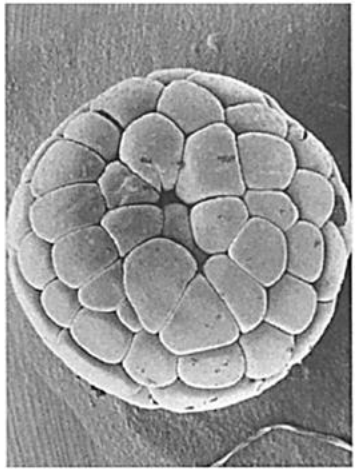
La cellula inizia a dividersi, mediante un leggero invaginamento della superficie cellulare, **il solco di clivaggio**



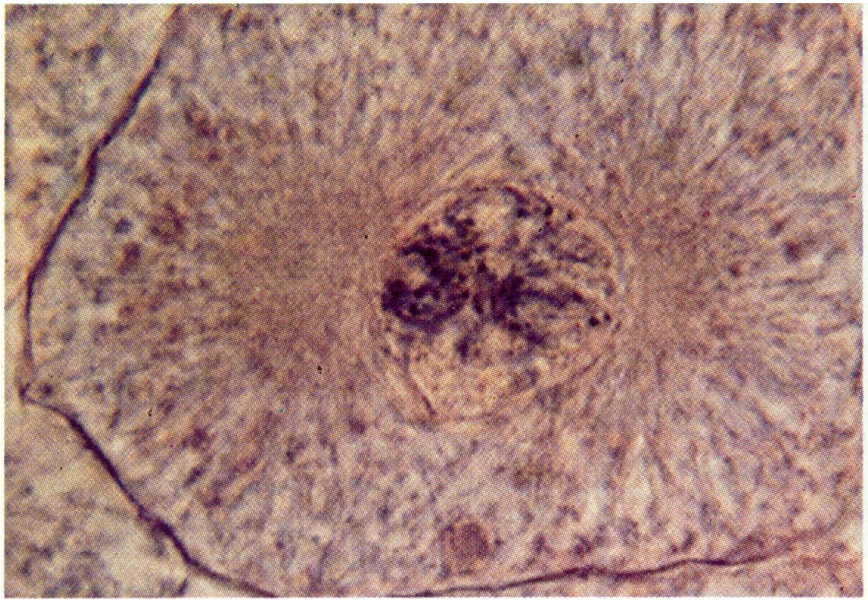


solco di clivaggio





Il clivaggio e' determinato da un fascio di filamenti, **anello contrattile**, formato da **filamenti di actina.** L'interazione dell'actina con la miosina determina una forza sufficiente a stringere l'anello e a dividere in due la cellula.

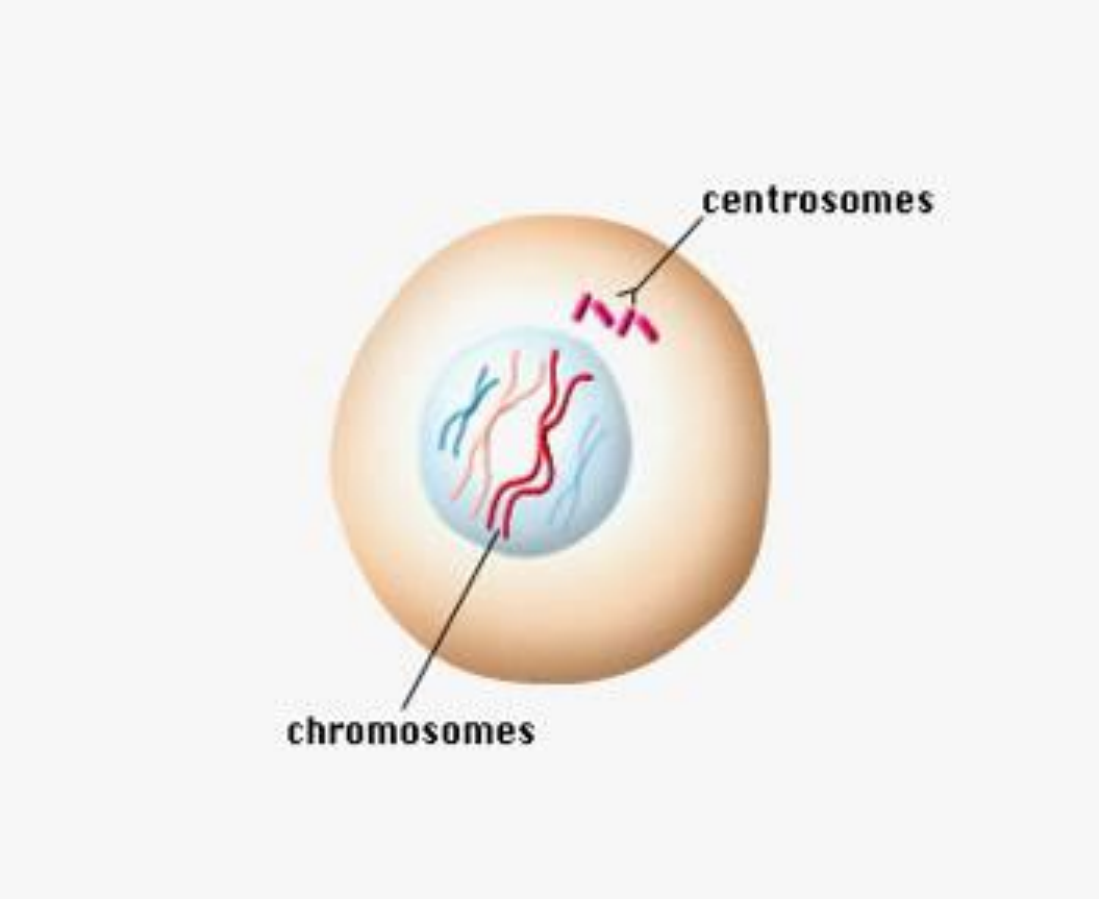


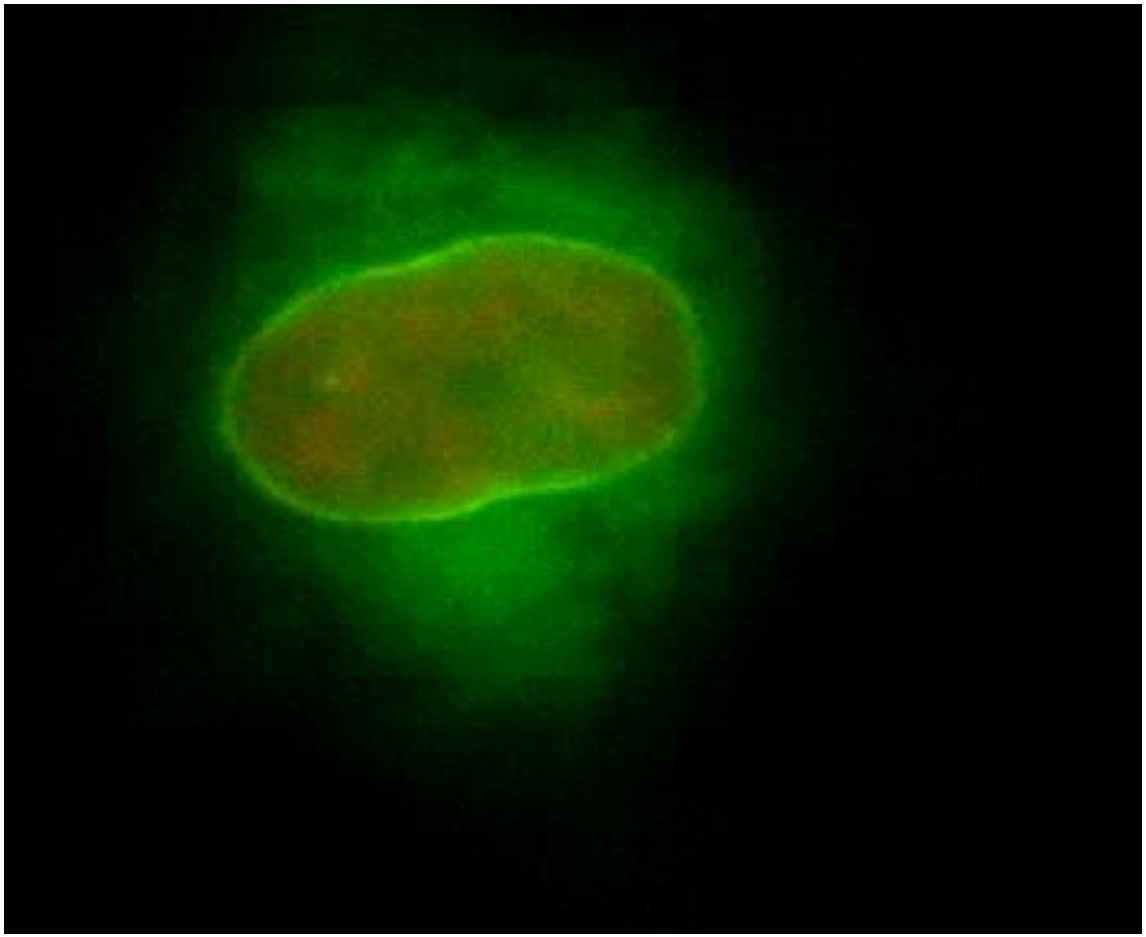
Profase

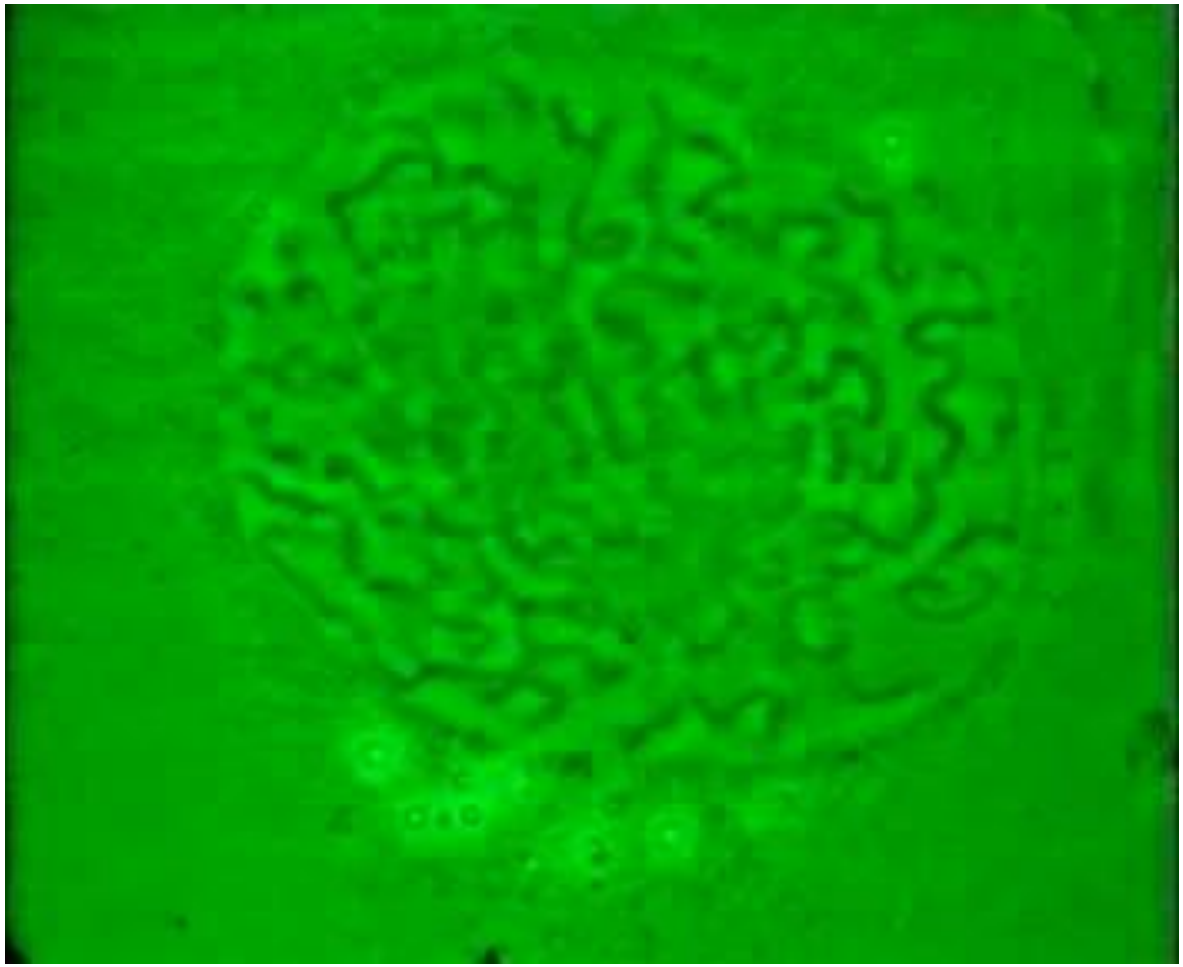
Metafase

Anafase

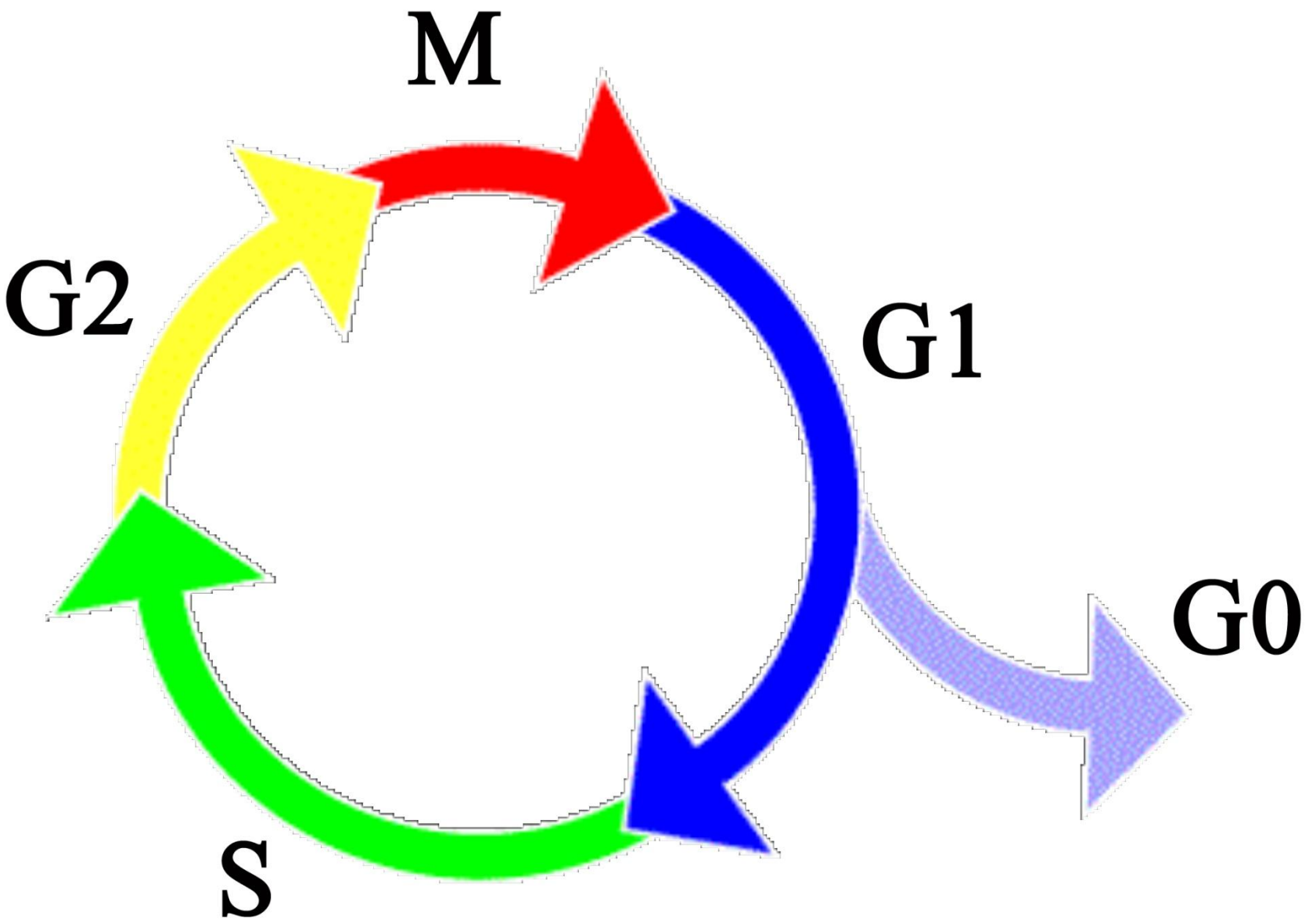
Telofase


centrosomes
chromosomes





Il ciclo cellulare



G0

- Una cellula puo' uscire dal ciclo cellulare temporaneamente oppure permanentemente.
- Esce dalla fase G1 ed entra in uno stadio chiamato G0
- Una cellula in G0 e' spesso definita quiescente → svolge importanti funzioni per l'org

SECREZIONE

CONDUZIONE DELL'IMPULSO NERVOSO

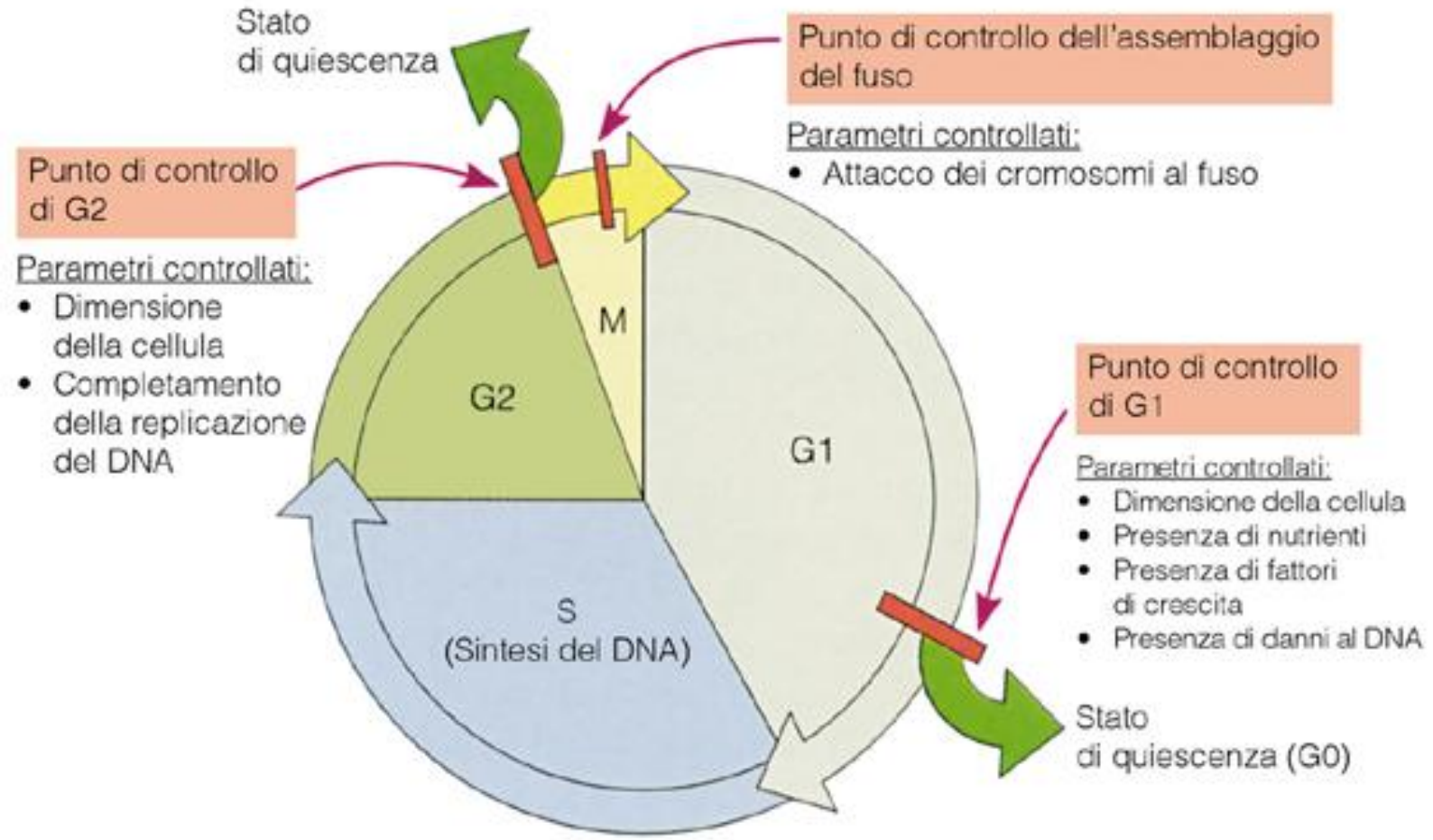
DIFESA DELL'ORGANISMO - ATTACCO AI PATOGENI

- Spesso cellule in G0 → terminalmente differenziate
- Non rientrano nel ciclo cellulare
- Svolgono funzioni nell'organismo fino alla morte

- Altre cellule in G0 possono rientrare nel ciclo cellulare.
- La maggior parte dei linfociti umani sono in G0 → rientrano nel ciclo cellulare alla fase

↑ stimolo

CONTROLLO DEL CICLO CELLULARE



La cellula e' in grado in ogni momento di monitorare il ciclo cellulare

Il controllo si basa su segnali chimici che riflettono sia le condizioni intracellulari che ambientali

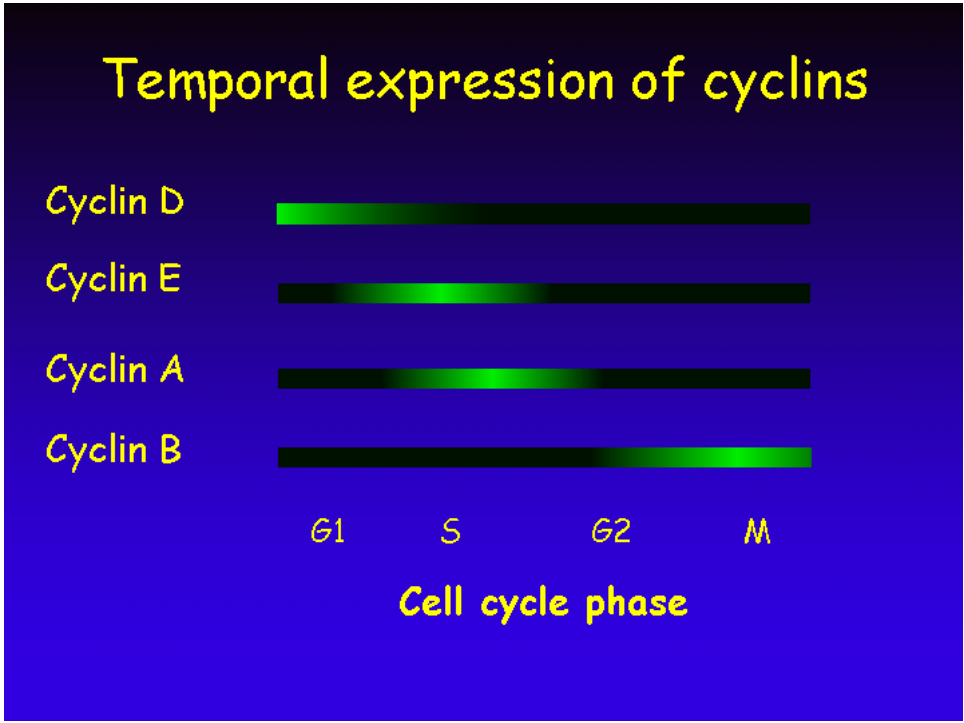
Il passaggio di una cellula attraverso le fasi del ciclo cellulare e' controllato da proteine presenti nel citoplasma:gli **MPF** o **chinasi ciclina-dipendenti**, presenti in tre gruppi

- **G1 CDKs**
- **Fase S CDKs**
- **Fase M CDKs**

Le **cicline** sono proteine in grado di attivare le **Kinasi ciclina/dipendenti.**
La **concentrazione delle cicline** aumenta (o diminuisce) in relazione alle fasi del ciclo cellulare.

Le **cicline** sono divise in 3 gruppi:

- **cicline della fase G1**
- **cicline della fase S**
- **cicline della fase M**



The Nobel Prize in Physiology or Medicine

8 October 2001

“for their discoveries of key regulators of the cell cycle"

Leland H. Hartwell

Fred Hutchinson
Cancer Research Center
Seattle, WA, USA
(1939)

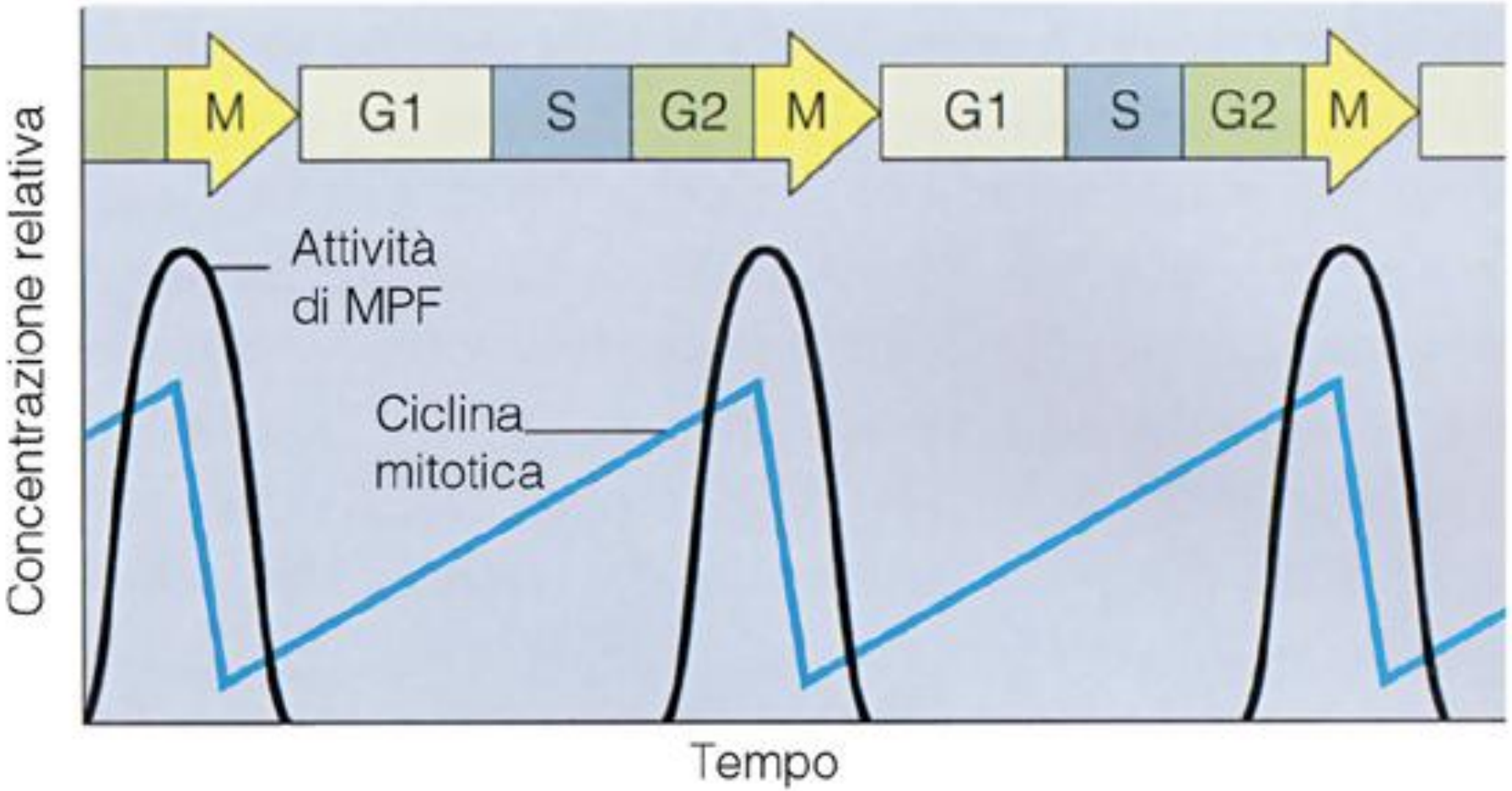
R. Timothy (Tim) Hunt

Imperial Cancer Research Fund
London, Great Britain
(1943)

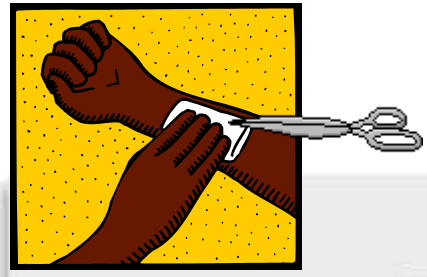
Paul M. Nurse

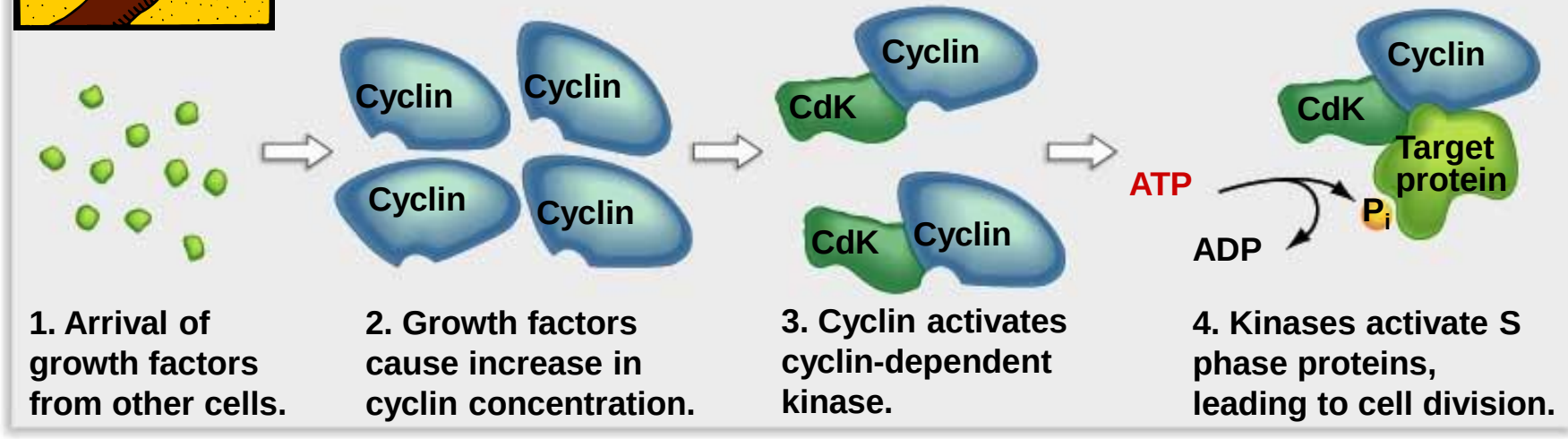
Imperial Cancer Research Fund
London, Great Britain
(1949)

Fluttuazione dei livelli di ciclina mitotica e dell'attivita' di MPF durante il ciclo cellulare



GROWTH FACTORS ARE INVOLVED IN PASSING THE G_1 CHECKPOINT



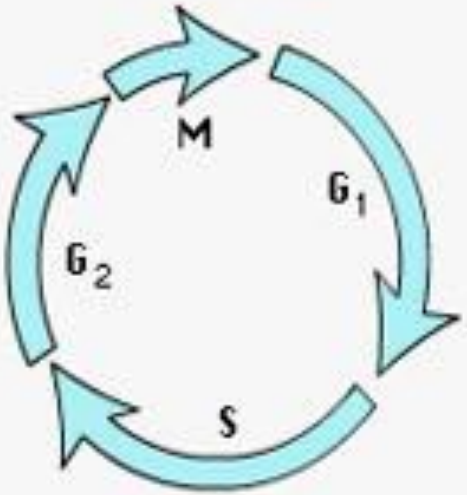


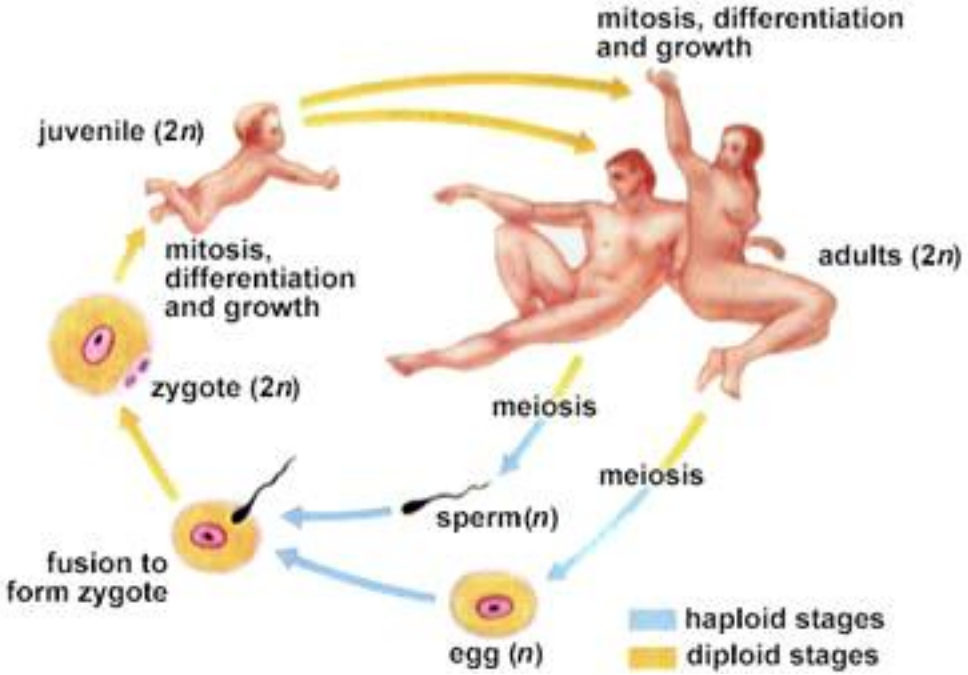
1. Arrival of growth factors from other cells.

2. Growth factors cause increase in cyclin concentration.

3. Cyclin activates cyclin-dependent kinase.

4. Kinases activate S phase proteins, leading to cell division.


M
G1
S
G2

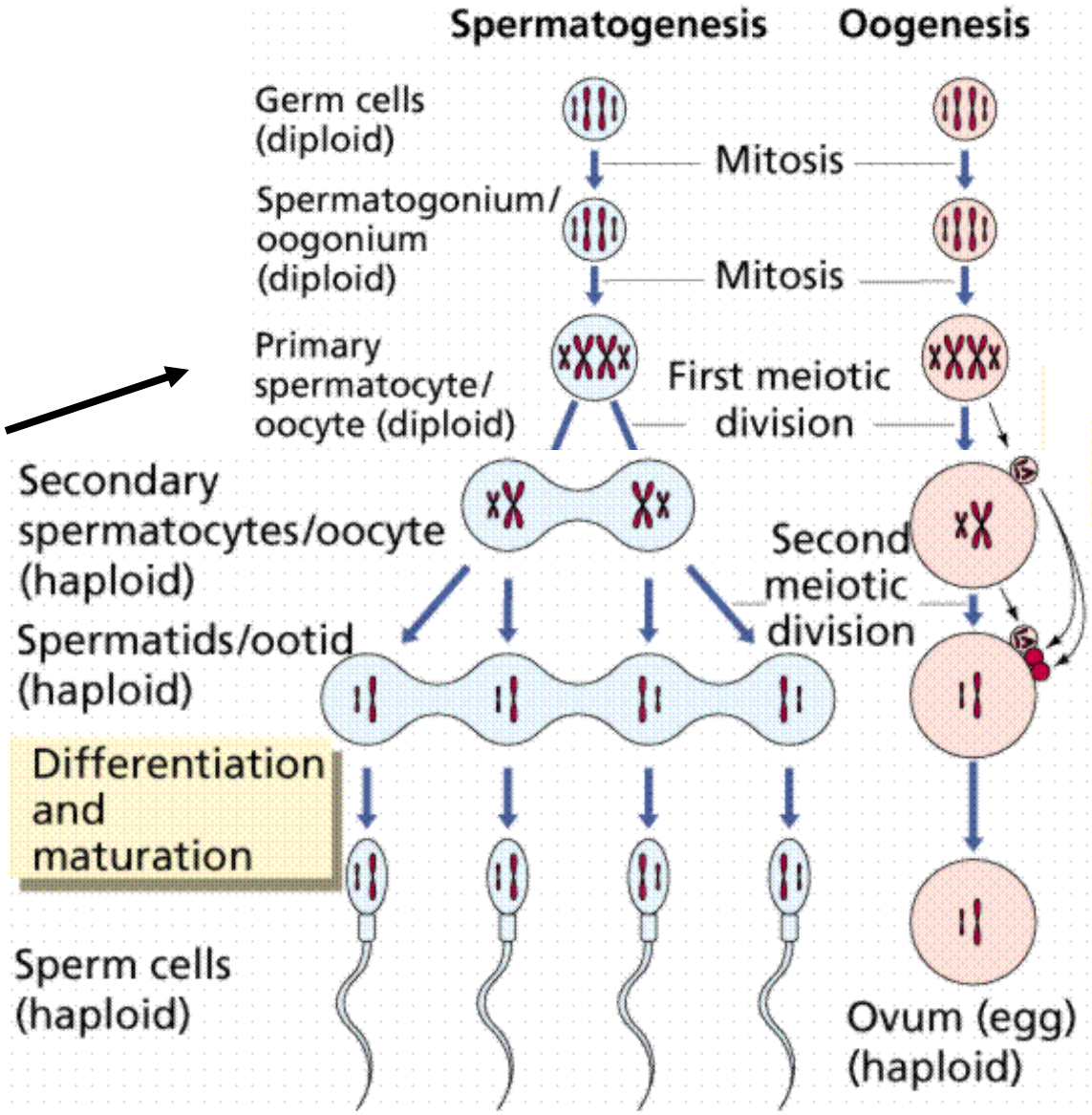


Life cycles are a diagrammatic representation of the events in the organism's development and reproduction. When interpreting life cycles, pay close attention to the ploidy level of particular parts of the cycle and where in the life cycle meiosis occurs. For example, animal life cycles have a dominant diploid phase, with the gametic (haploid) phase being a relative few cells. Most of the cells in your body are diploid, germ line diploid cells will undergo meiosis to produce gametes, with fertilization closely following meiosis.

Gametogenesis

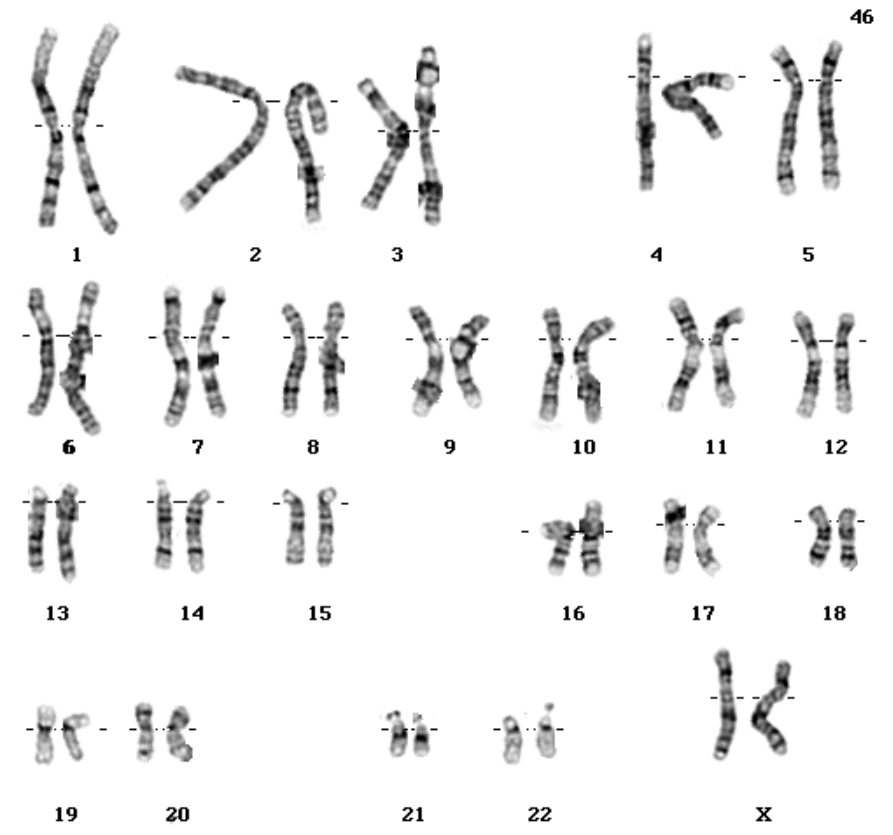
- The process of forming gametes from diploid cells of the germ line.
- Spermatogenesis is the process of forming sperm cells by meiosis (in animals, by mitosis in plants) in specialized organs known as gonads (in males these are termed testes).
- After division the cells undergo differentiation to become sperm cells.
- Oogenesis is the process of forming an ovum (egg) by meiosis (in animals, by mitosis in the gametophyte in plants) in specialized gonads known as ovaries.
- Whereas in spermatogenesis all 4 meiotic products develop into gametes, oogenesis places most of the cytoplasm into the large egg. The other cells, the polar bodies, do not develop. All the cytoplasm and organelles go into the egg.
- Human males produce 200,000,000 sperm per day, while the female produces one egg (usually) each menstrual cycle.

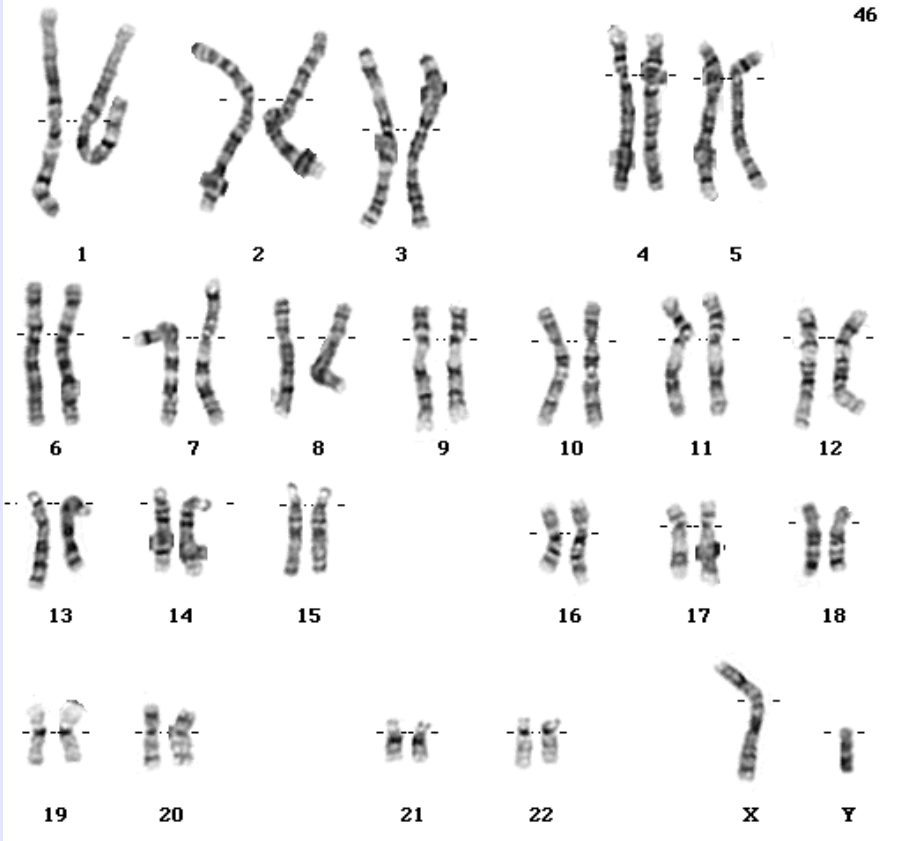
Meiosis



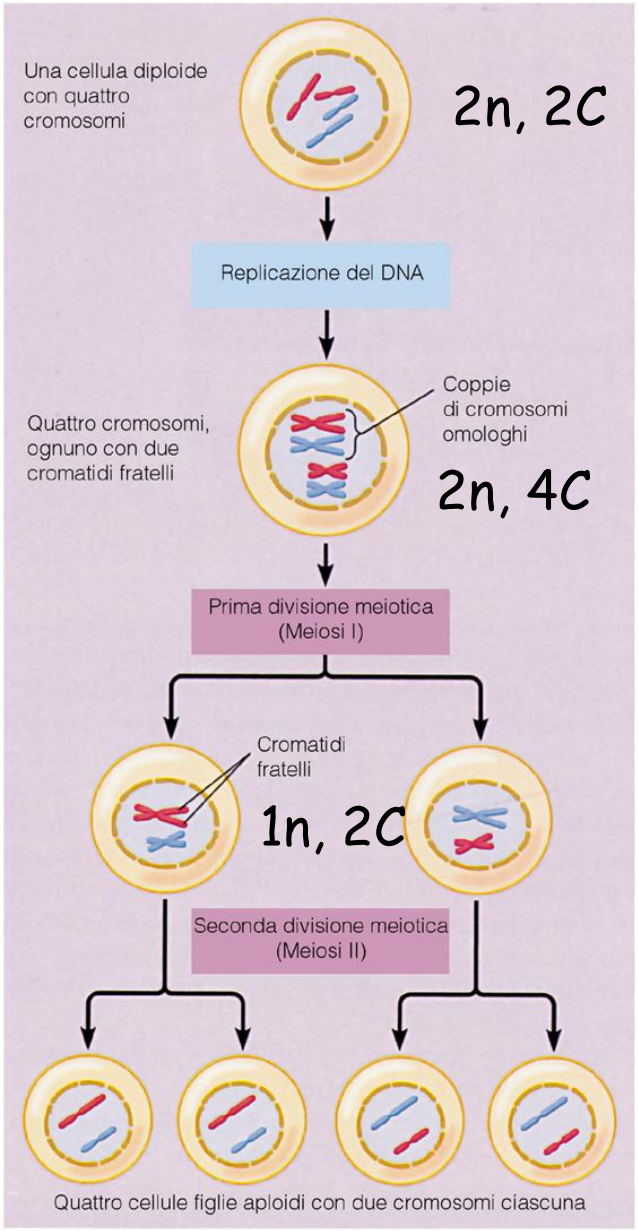
Differentiation and growth

Human chromosomes 2n=46





Meiosis



1n, 1C

Ploidia: numero di set di cromosomi presenti in una cellula

Diploide (2n): 2 sets di cromosomi
Contenuno in DNA 2C

Aploide (n): 1 set di cromosomi
Contenuto in DNA 1C

Phases of Meiosis

Two successive nuclear divisions occur, Meiosis I (Reduction) and Meiosis II (Division). Meiosis produces 4 haploid cells. Mitosis produces 2 diploid cells. The old name for meiosis was eduction/ division.

- Meiosis I reduces the ploidy level from 2n to n (reduction)
- Meiosis II divides the remaining set of chromosomes in a mitosis-like process (division).

Most of the differences between the processes occur during Meiosis I.

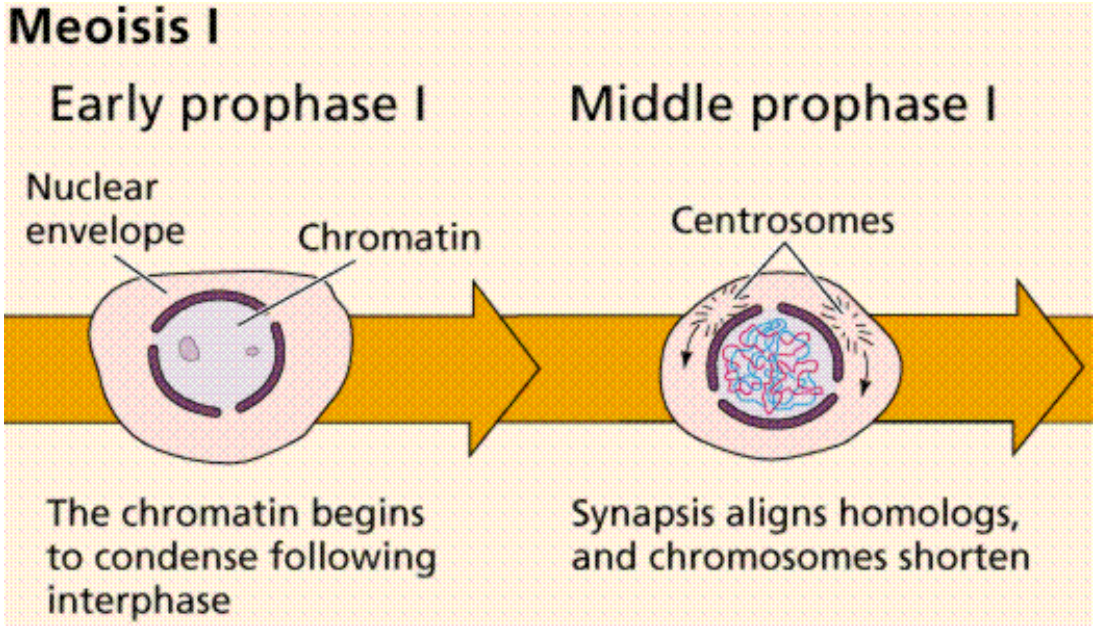
Durante il processo meiotico, si susseguono due divisioni cellulari

Le tappe di divisione cellulare sono definite dal susseguirsi di:

Profase
Metafase
Anafase
Telofase e citodieresi

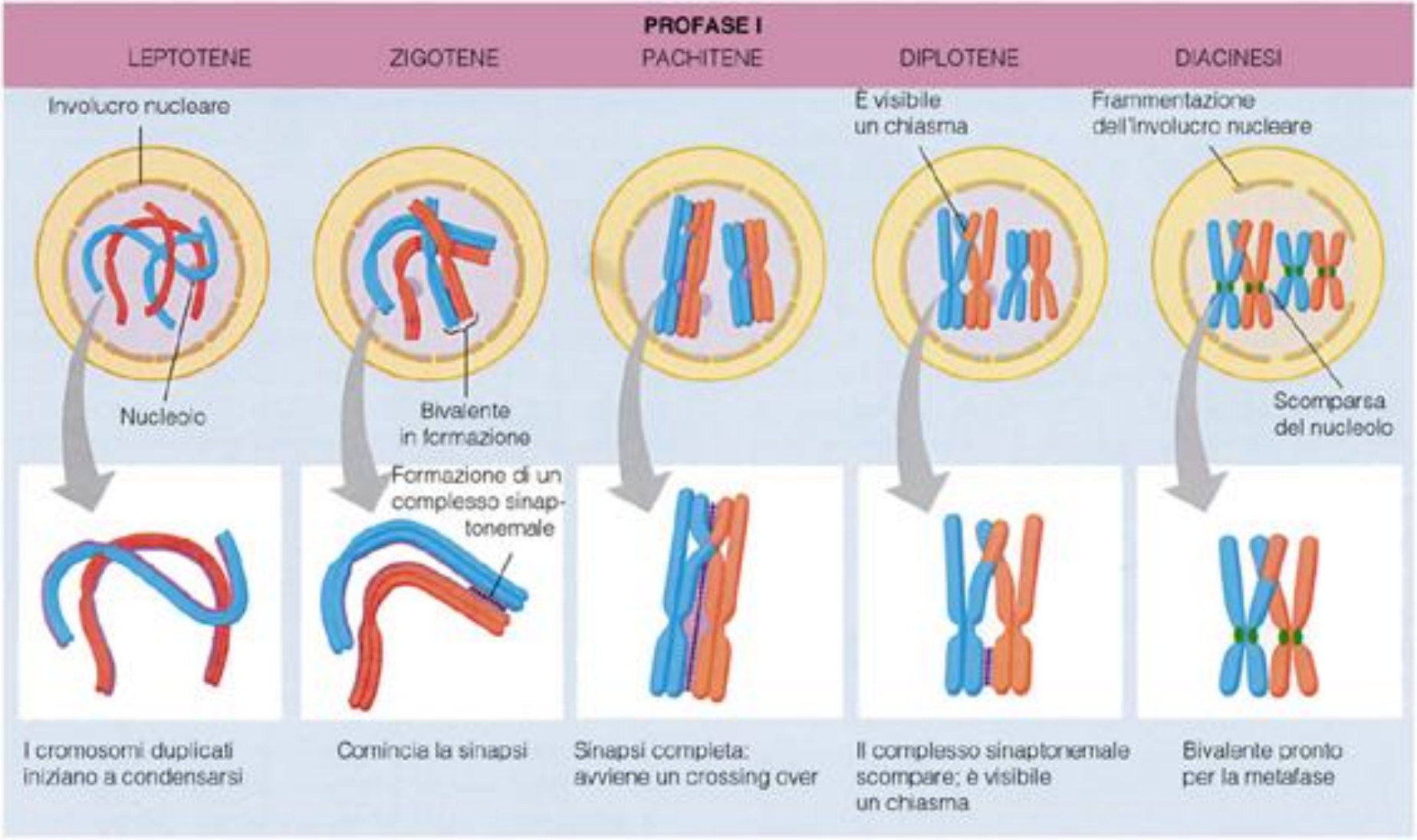
Durante la profase della prima divisione meiotica avviene il processo di **ricombinazione genetica**

La profase I puo' essere molto lunga, nel caso della cellula germinale femminile, inizia durante la fase fetale dello sviluppo e termina con l'ovulazione dell'oocita, durante la vita adulta dell'individuo



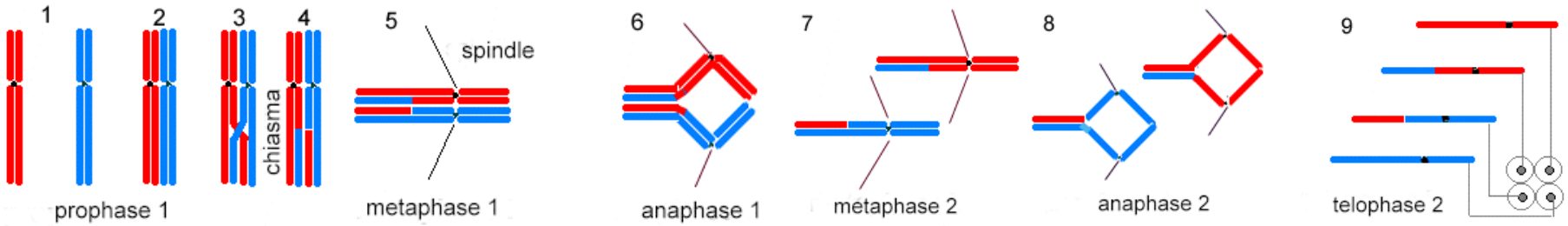
Events of Prophase I (save for synapsis and crossing over) are similar to those in prophase of mitosis:

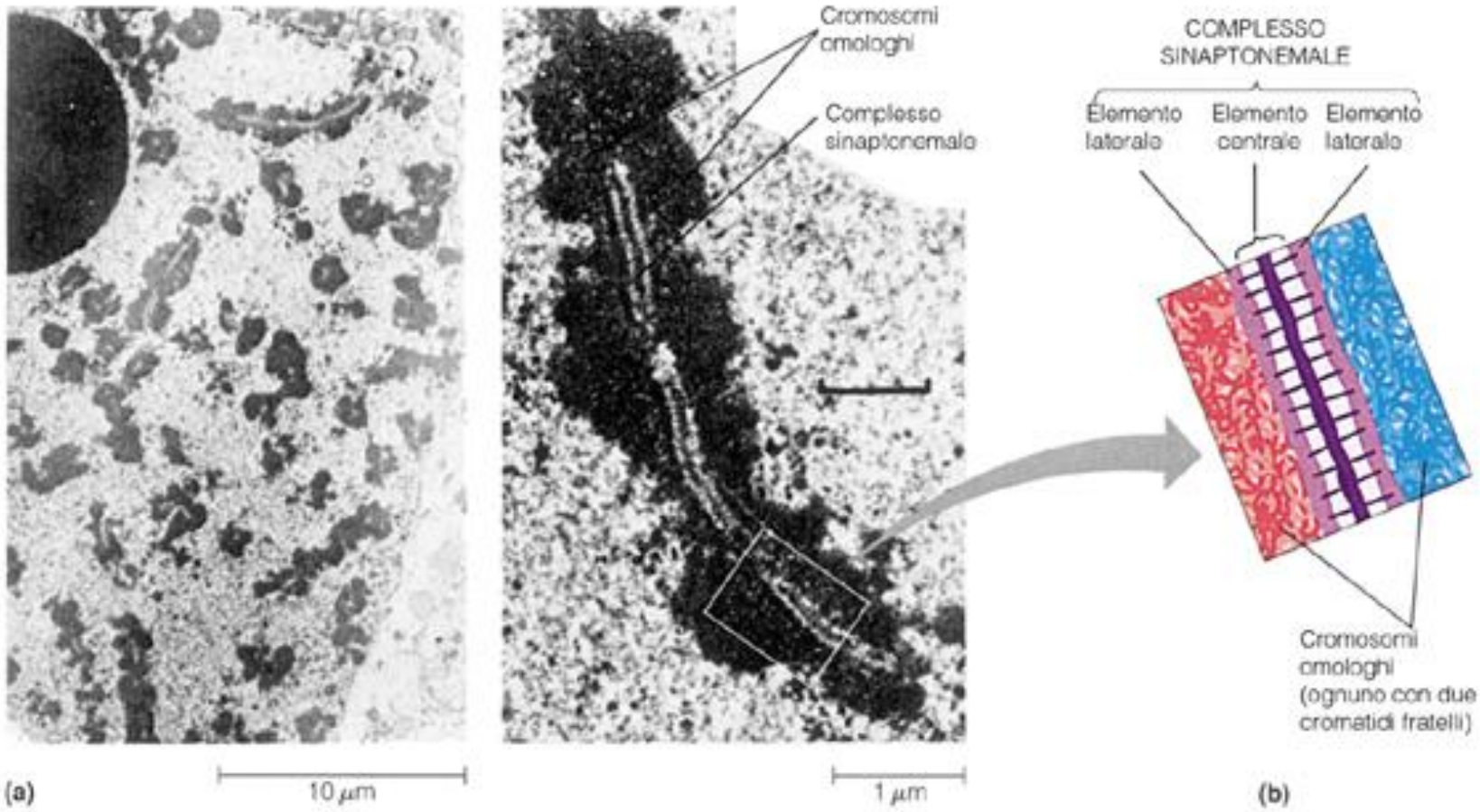
- chromatin condenses into chromosomes (bivalents)
- the nucleolus dissolves
- nuclear membrane is disassembled
- the spindle apparatus forms



La I profase puo' essere divisa in cinque stadi

- **Prophase I** has a unique event - the pairing (by an as yet undiscovered mechanism) of homologous chromosomes.
- **Synapsis** is the process of linking of the replicated homologous chromosomes.
- The resulting chromosome is termed a tetrad, being composed of two chromatids from each chromosome, forming a thick (4-strand) structure.
- **Crossing-over** may occur at this point.
- During crossing-over, **genetic recombination** occurs, chromatids break and may be reattached to a different homologous chromosome.

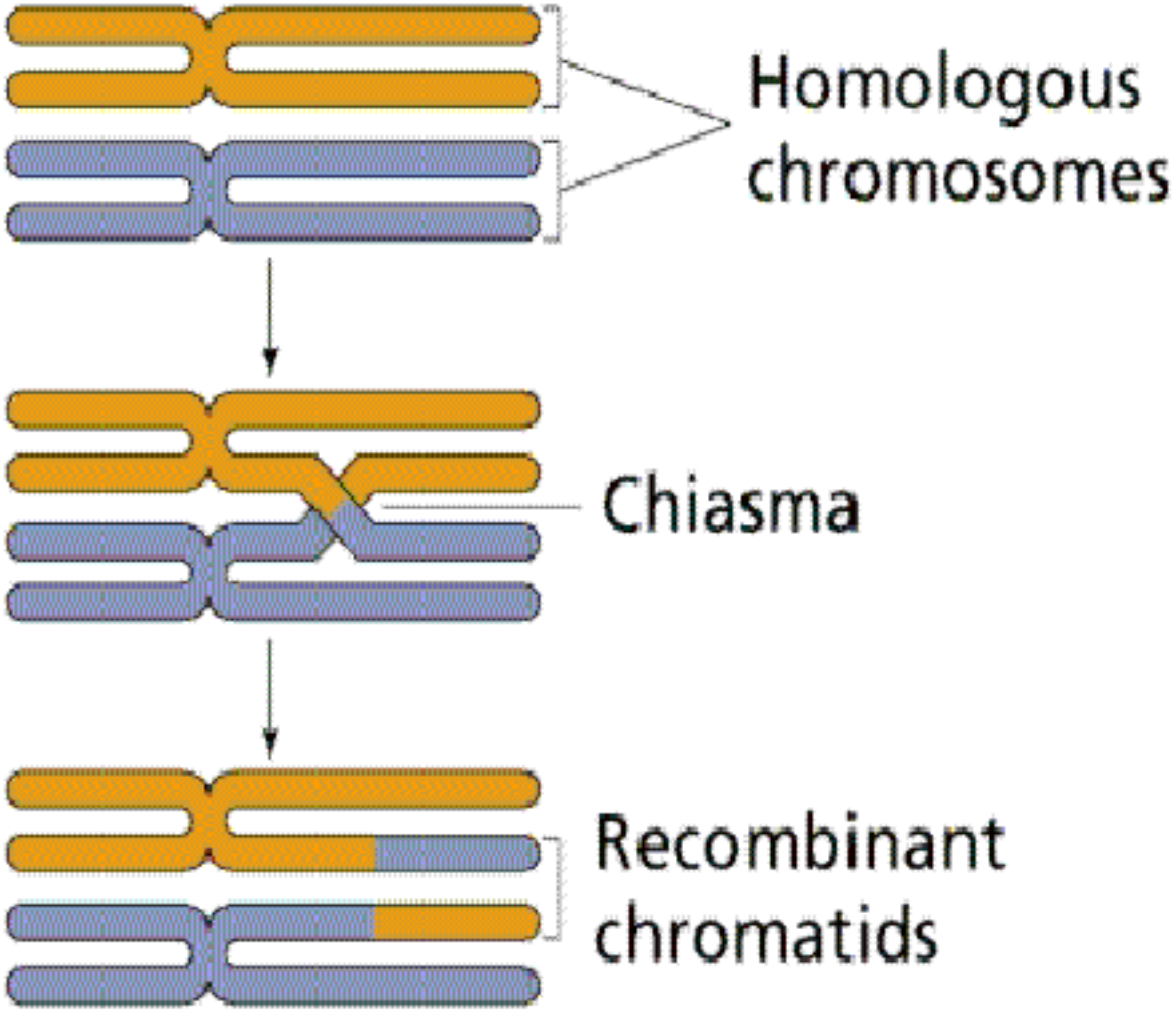




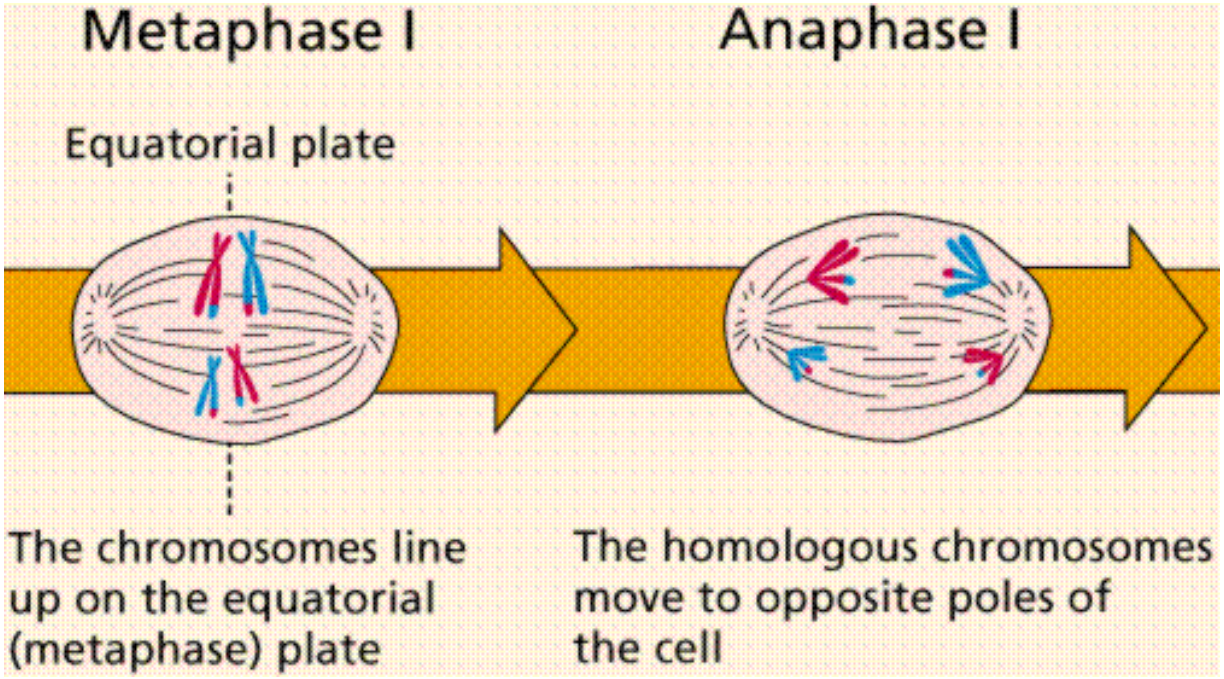
I cromosomi omologhi sono tenuti in stretto contatto dal **complesso sinaptonemale**

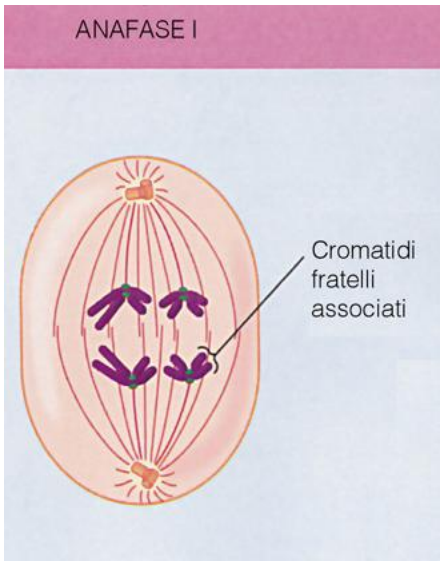
Negli eucarioti la formazione del complesso e' **in associazione con il processo di crossing-over**

La ricombinazione avviene **a livello dei noduli di ricombinazione**

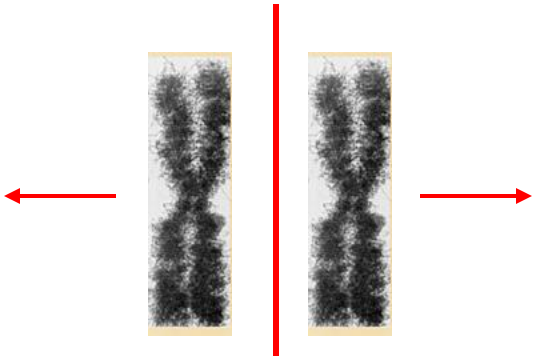


Crossing-over between homologous chromosomes produces chromosomes with new associations of genes and alleles.

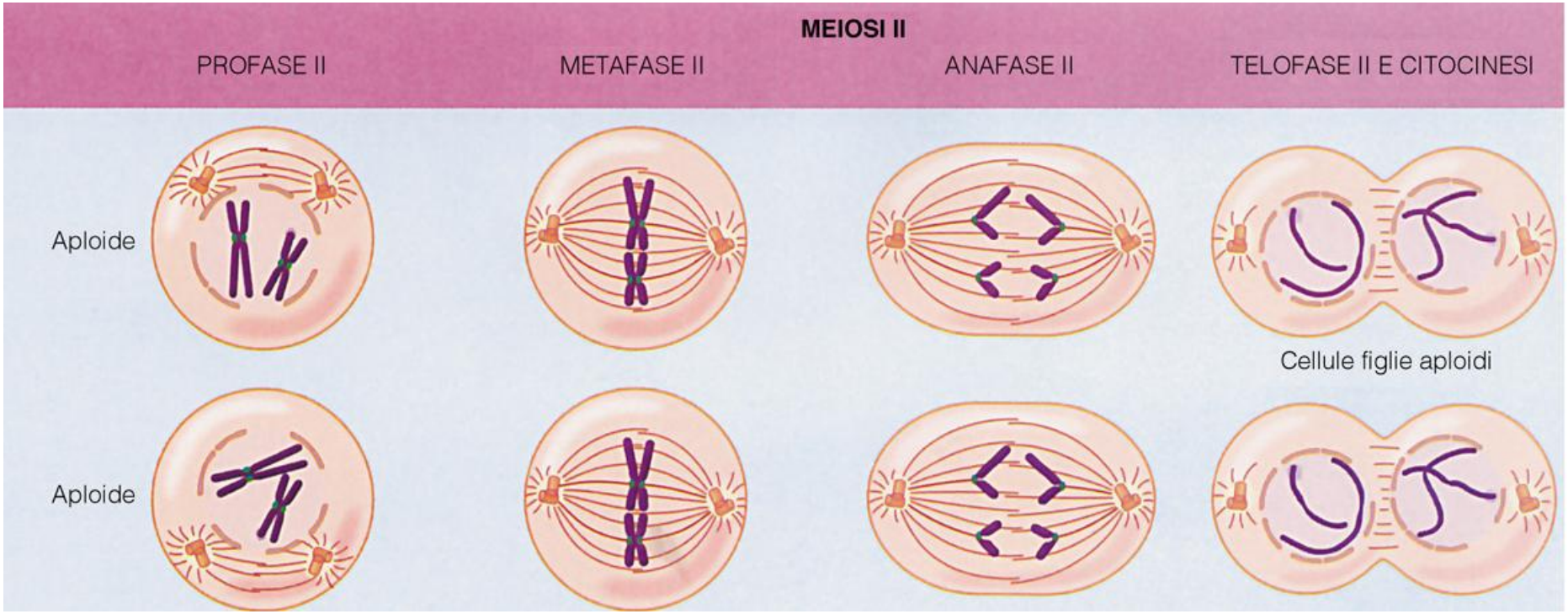


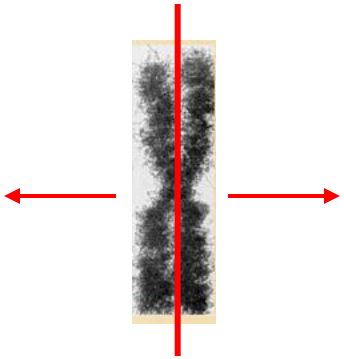


Anaphase I. Chiasmata separate. Chromosomes move to separate poles. Each of the daughter cells is now haploid (23 chromosomes), but each chromosome has two chromatids.

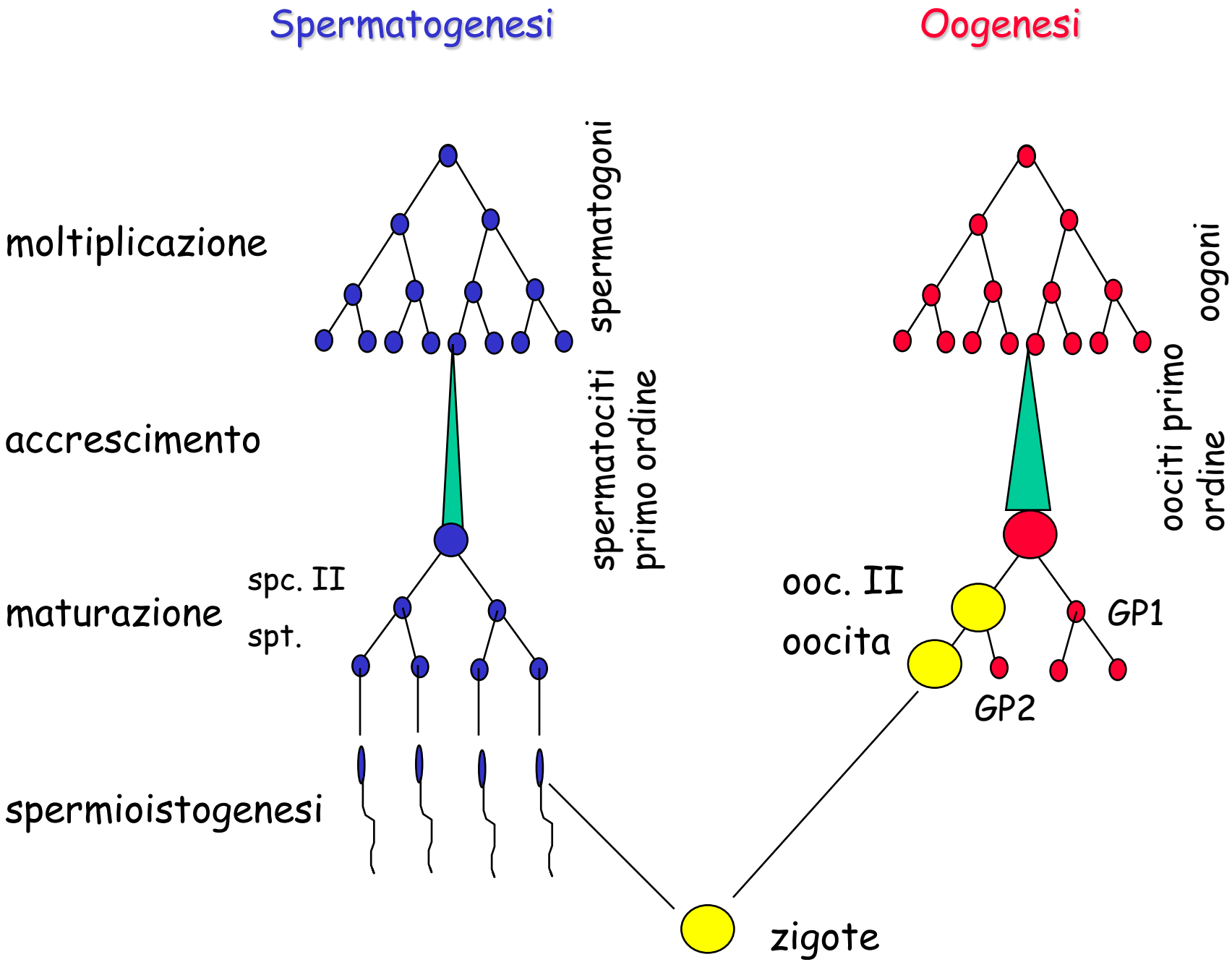


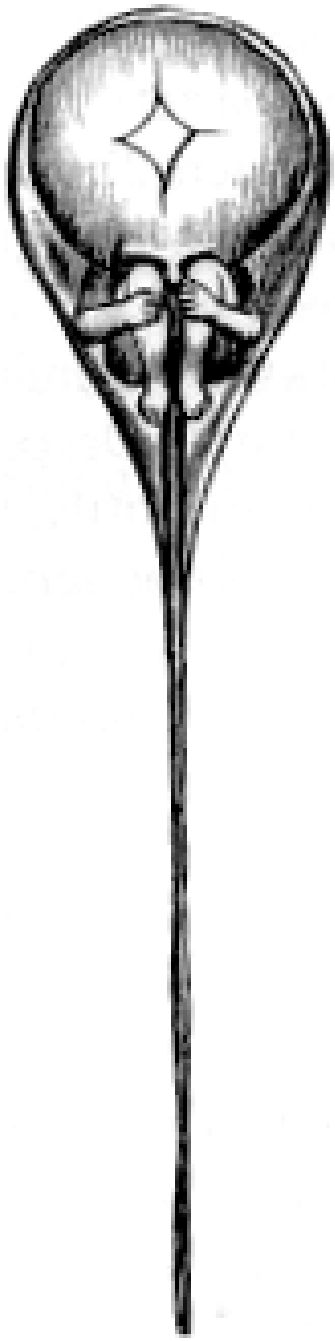
Schema riassuntivo della II divisione meiotica

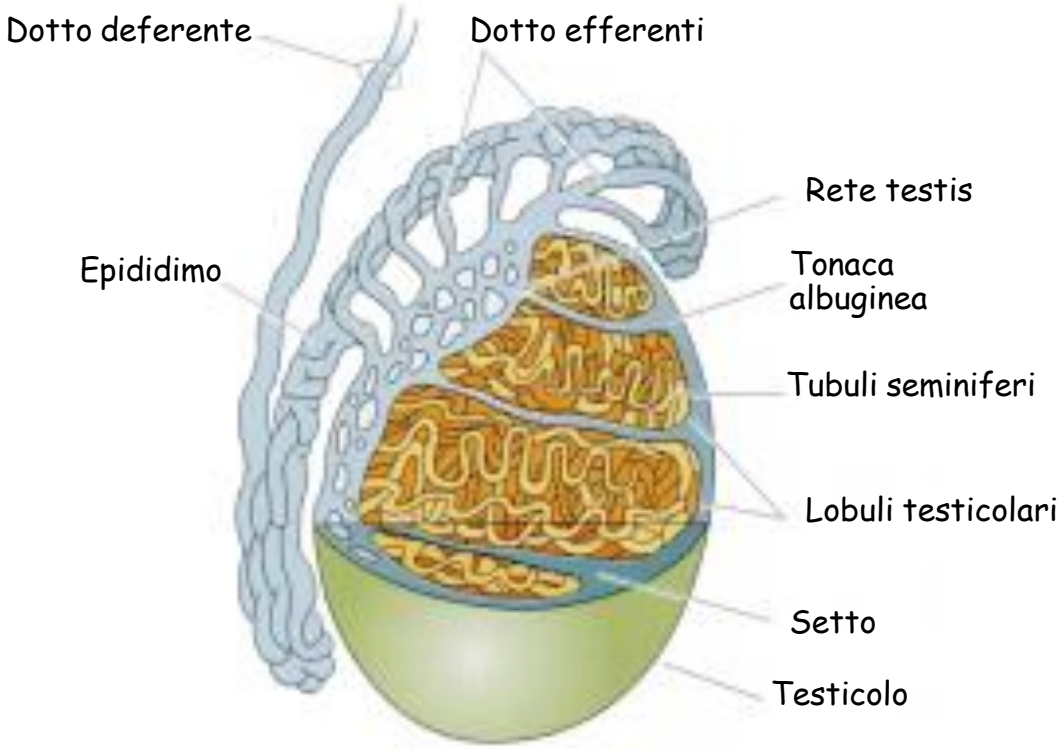




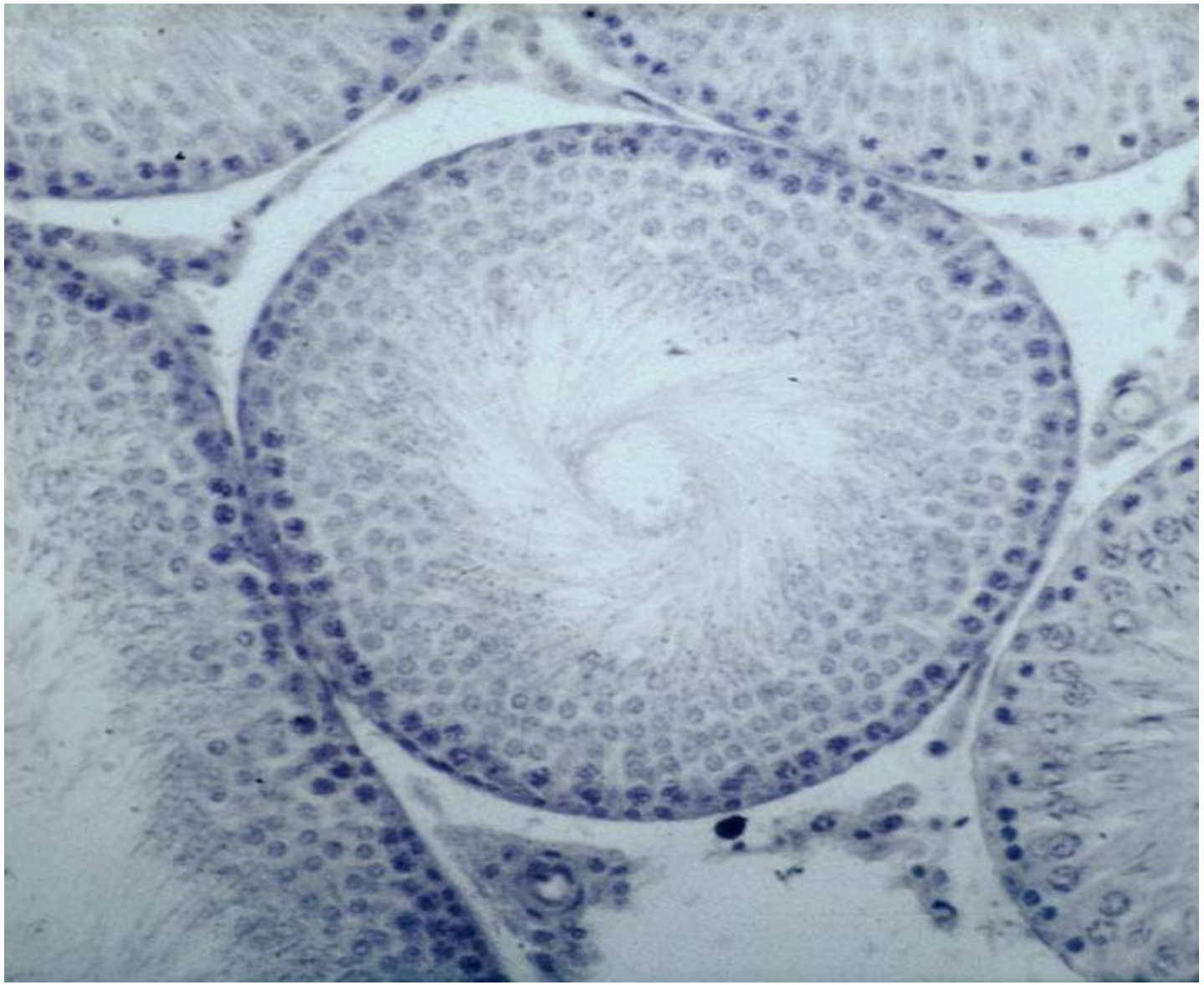

1'
1"
2'
2"

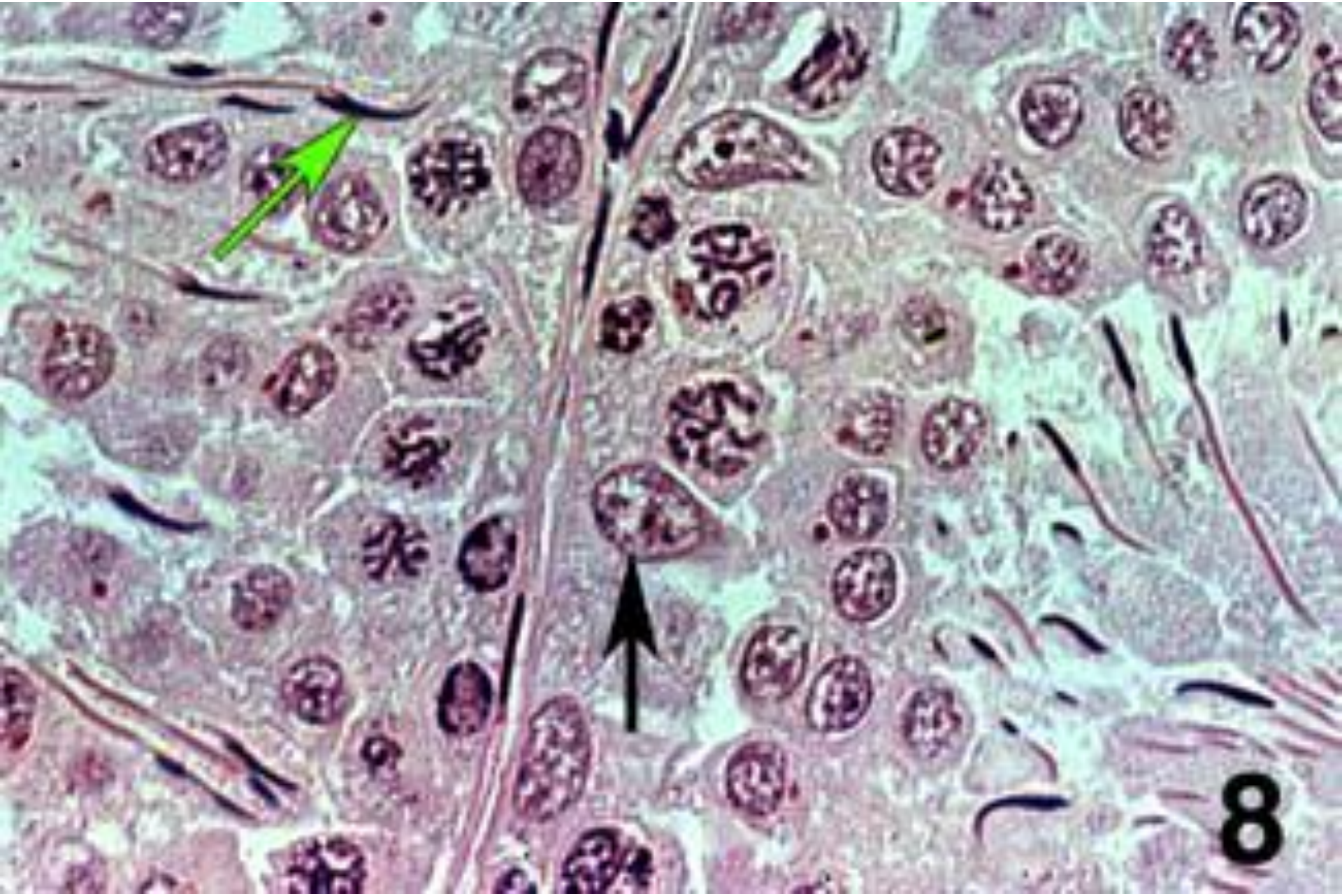

Spermatogenesi
Oogenesi
moltiplicazione
accrescimento
maturazione
spermioistogenesi
spermatogoni
spermatociti primo ordine
spc. II
spt.
oogoni
oociti primo ordine
ooc. II
oocita
GP1
GP2
zigote

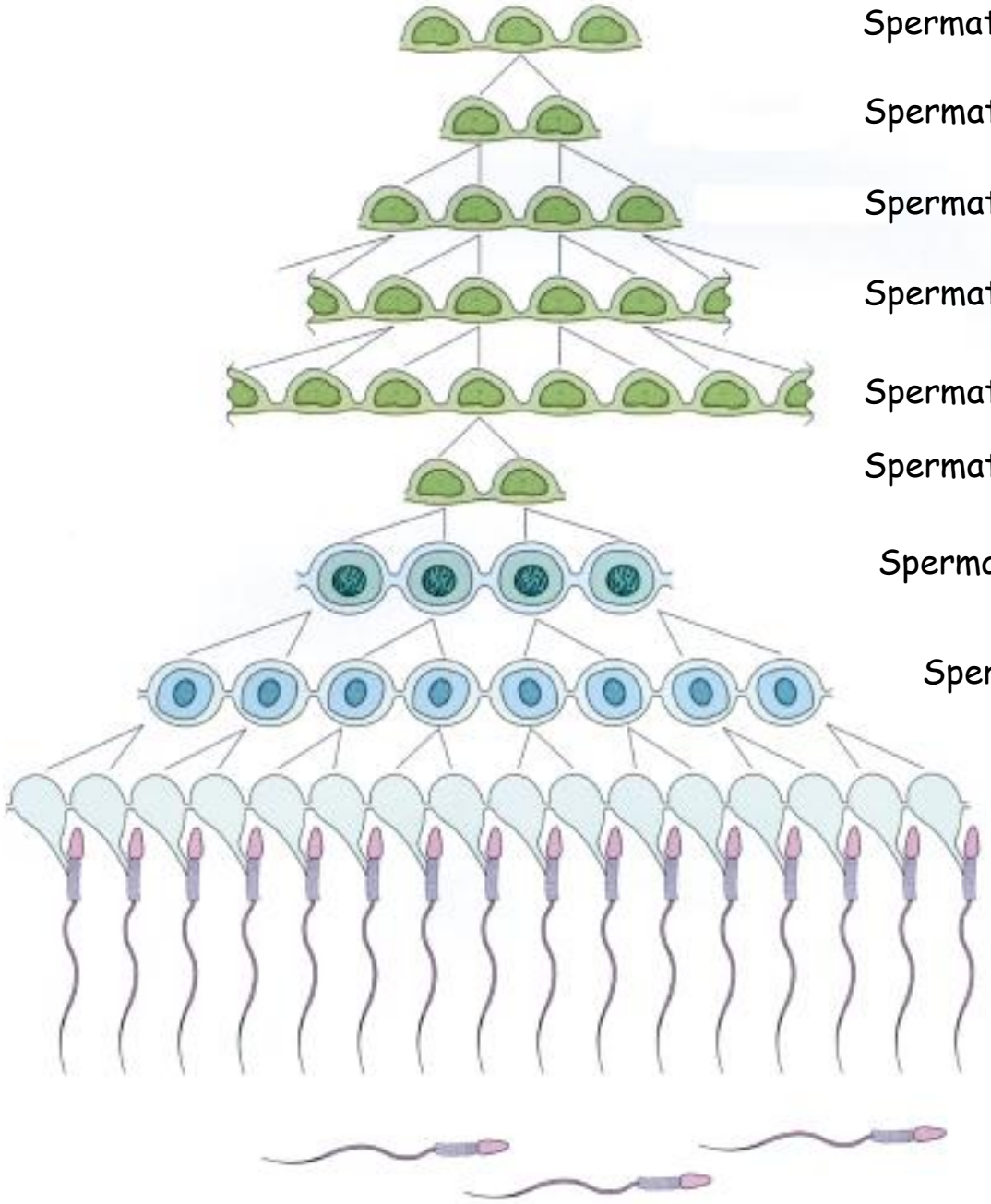


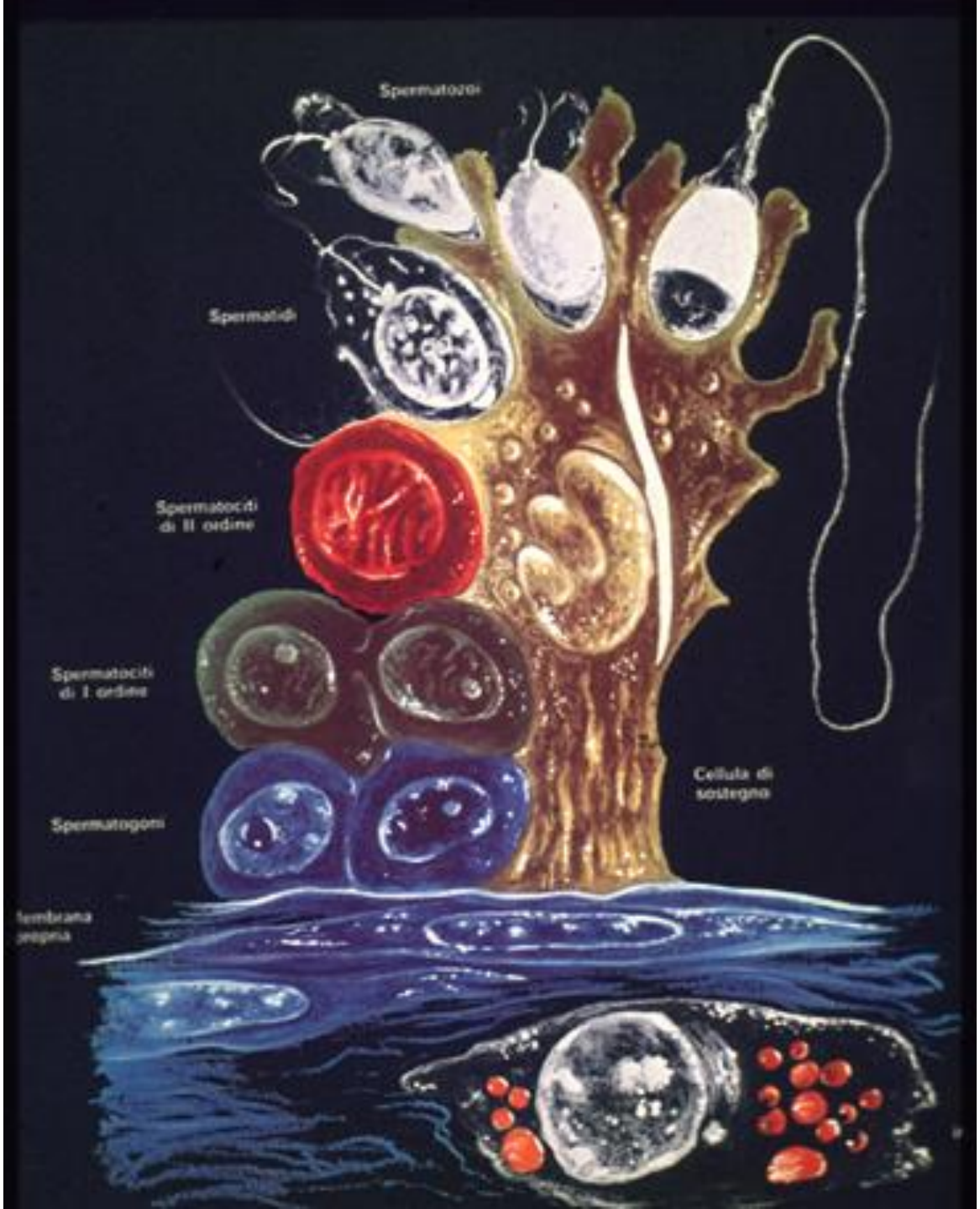

Dotto deferente
Dotto efferenti
Rete testis
Epididimo
Tonaca albuginea
Tubuli seminiferi
Lobuli testicolari
Setto
Testicolo

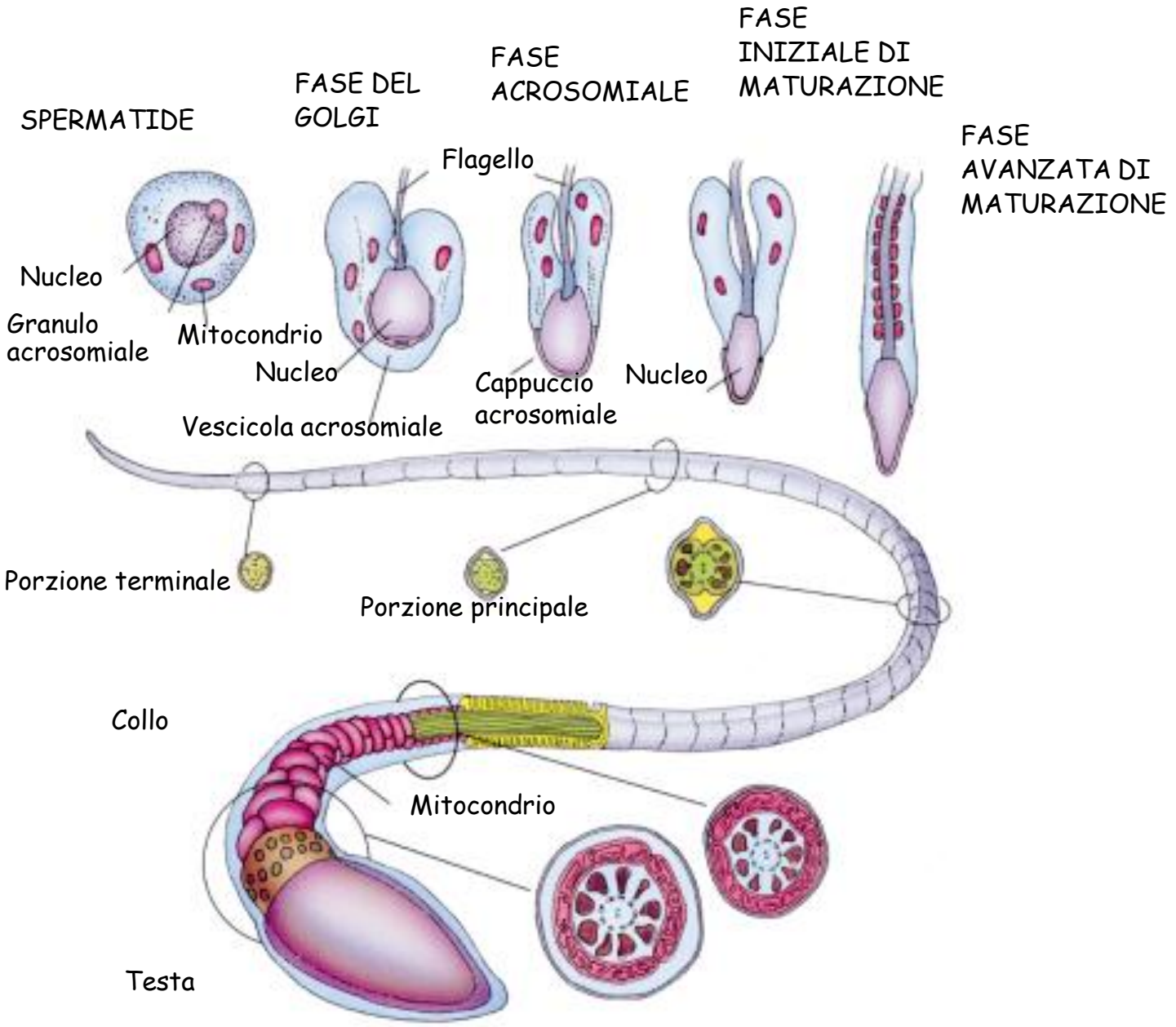
Camillo Golgi 1843 - 1926

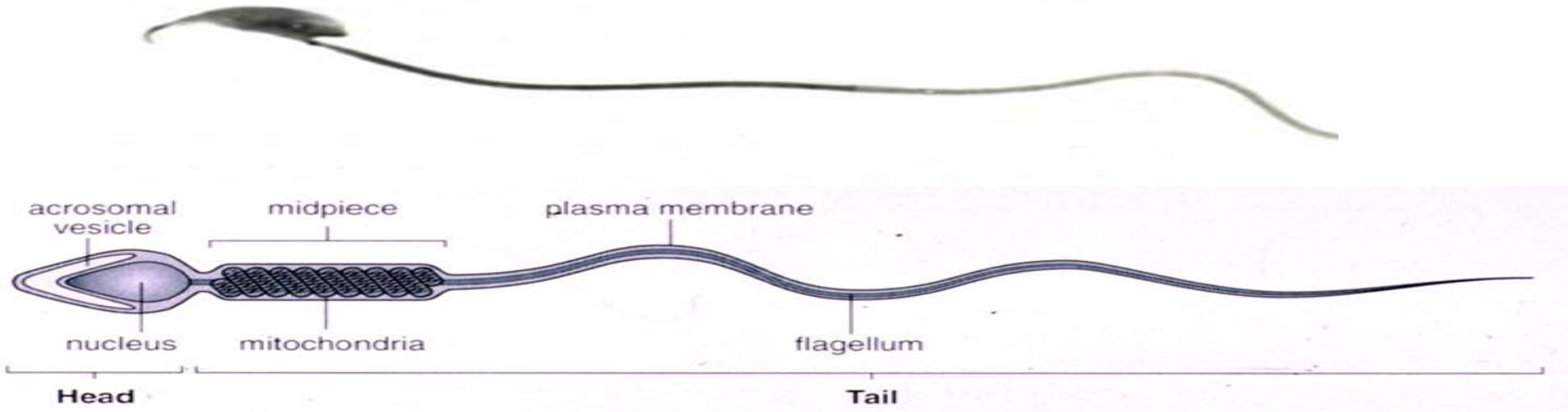



8


Spermatogoni A_1
Spermatogoni A_2
Spermatogoni A_3
Spermatogoni A_4
Spermatogoni intermedi
Spermatogoni B
Spermatociti I ordine
Spermatociti II ordine
Spermatidi
Spermatozoi maturi


Spermatozoi
Spermatidi
Spermatociti di II ordine
Spermatociti di I ordine
Spermatogoni
Cellula di sostegno


SPERMATIDE
FASE DEL GOLGI
FASE ACROSOMIALE
FASE INIZIALE DI MATURAZIONE
FASE AVANZATA DI MATURAZIONE
Flagello
Nucleo
Granulo acrosomiale
Mitocondrio
Nucleo
Vescicola acrosomiale
Cappuccio acrosomiale
Nucleo
Porzione terminale
Porzione principale
Collo
Mitocondrio
Testa



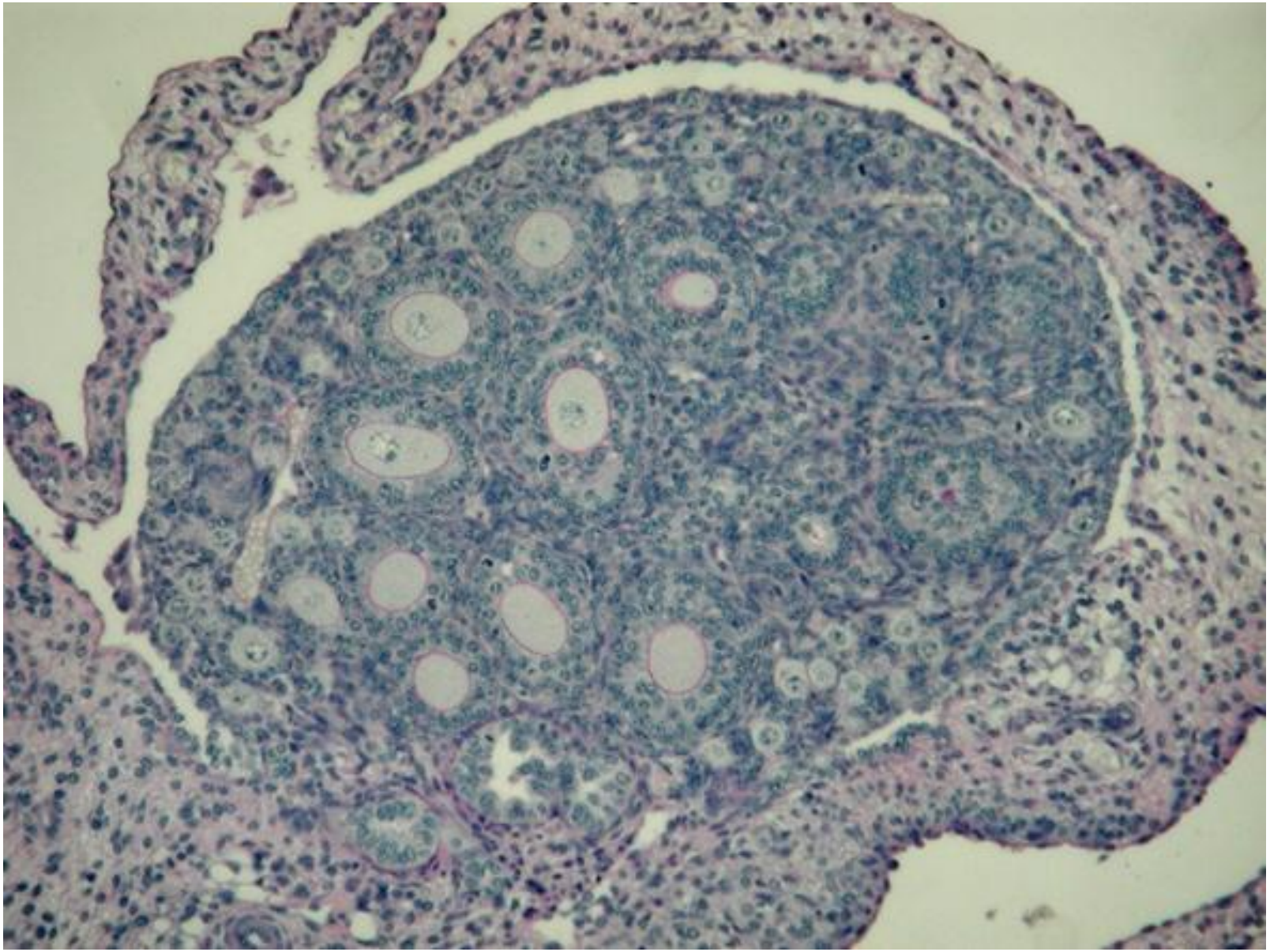
Lo spermatozoo presenta due porzioni principali: la testa (contenente il nucleo del gamete maschile) ed il flagello.

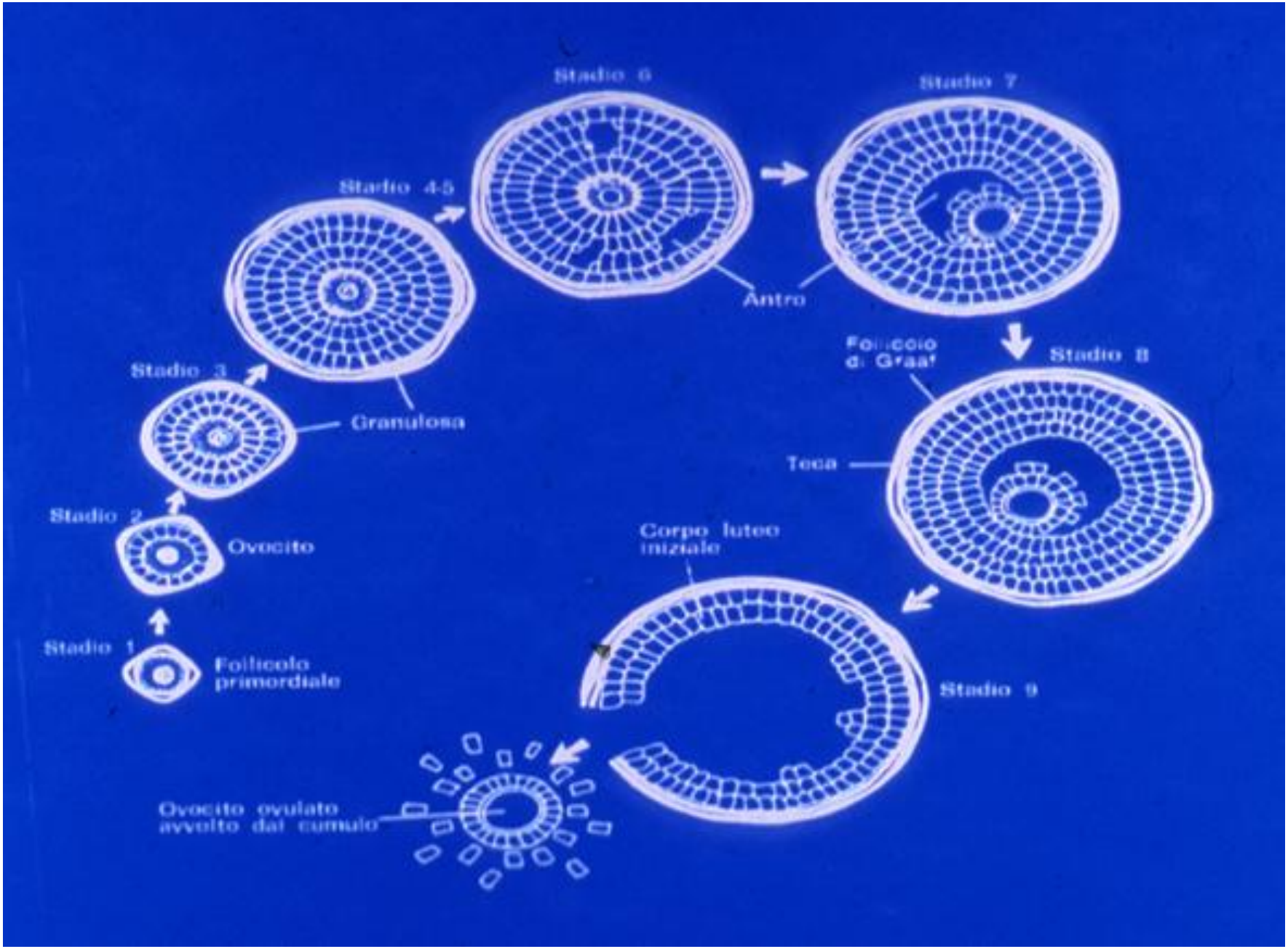
La testa e' ricoperta dall'acrosoma

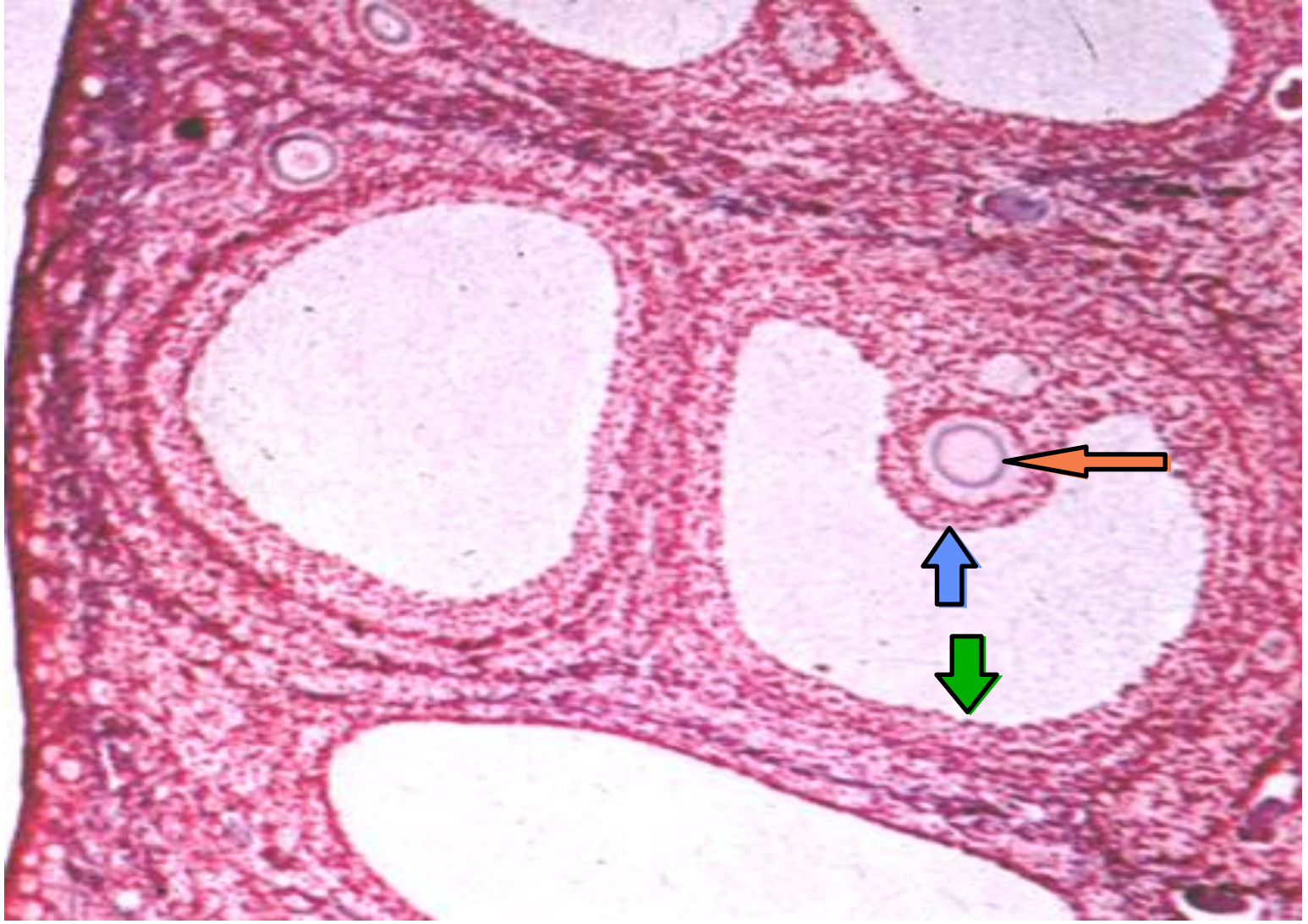
La porzione del flagello piu' vicina alla testa viene chiamata segmento mediano e contiene i mitocondri (sorgenti energetiche necessarie al movimento della coda)


OÖGENESIS
BOUTIQUE

1 week after birth, mouse




Stadio 6
Stadio 7
Stadio 4-5
Antro
Follicolo di Graaf
Stadio 8
Stadio 3
Granulosa
Teca
Stadio 2
Ovocito
Corpo luteo iniziale
Stadio 1
Follicolo primordiale
Stadio 9
Ovocito ovulato avvolto dal cumulo

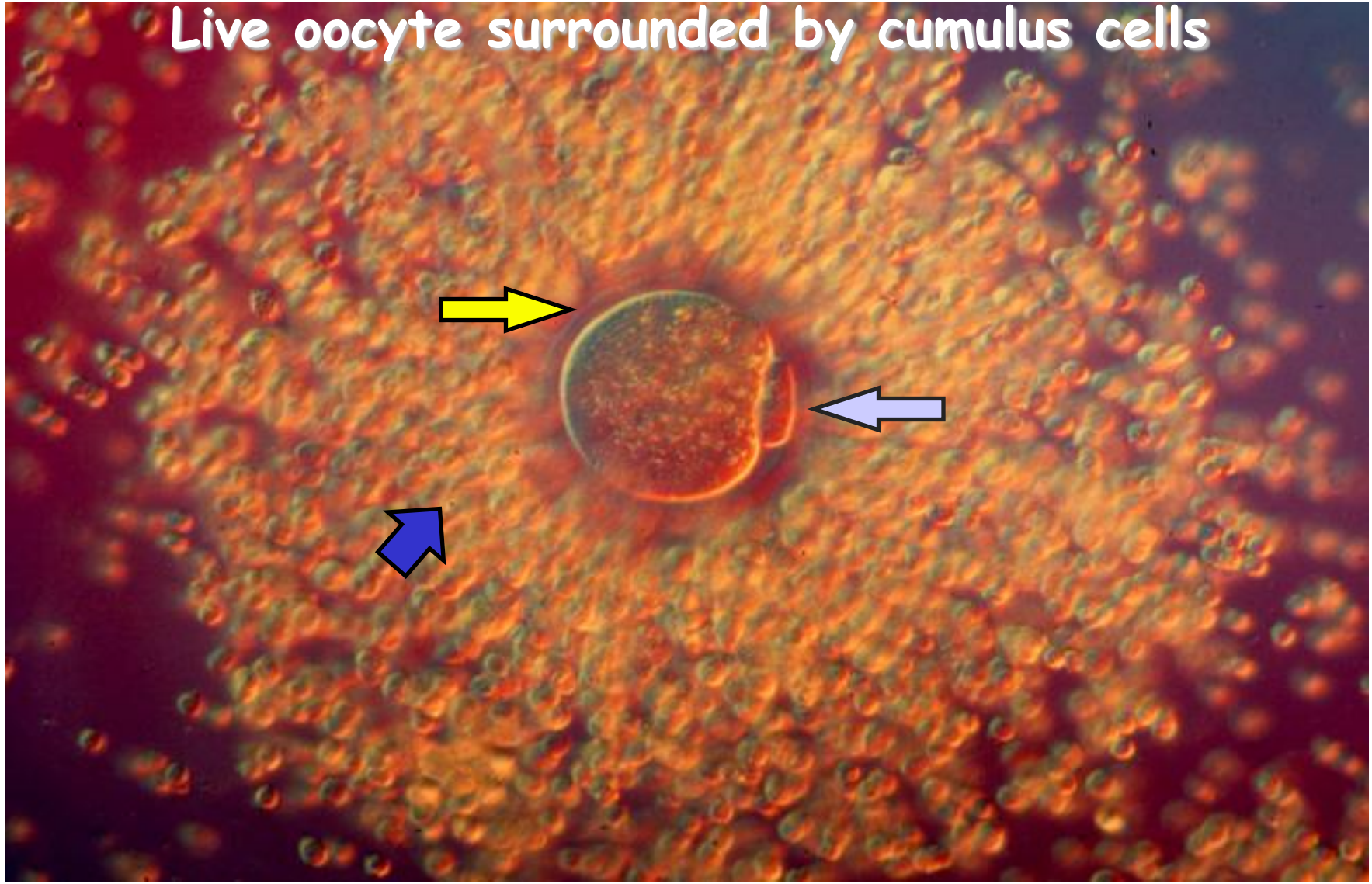


cumulo ooforo

oocita

granulosa

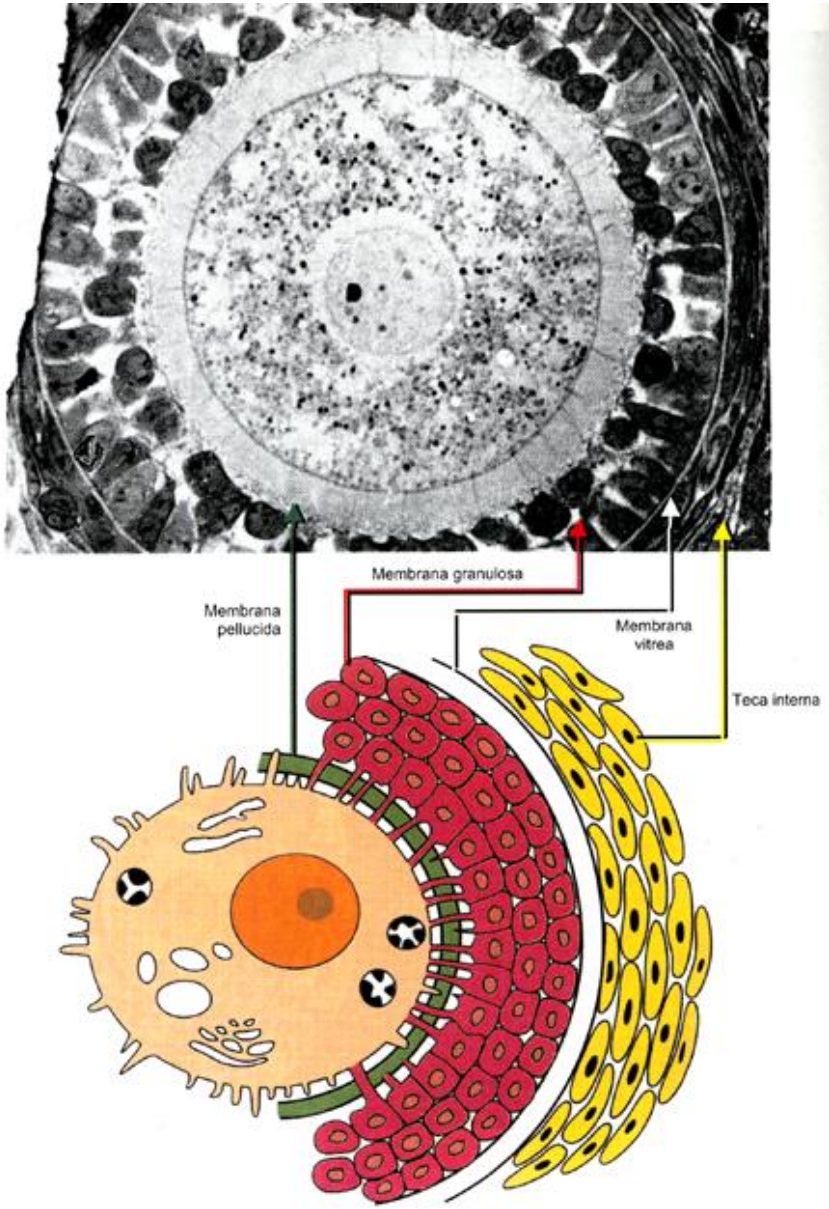
Live oocyte surrounded by cumulus cells



zona pellucida

Ist polar body

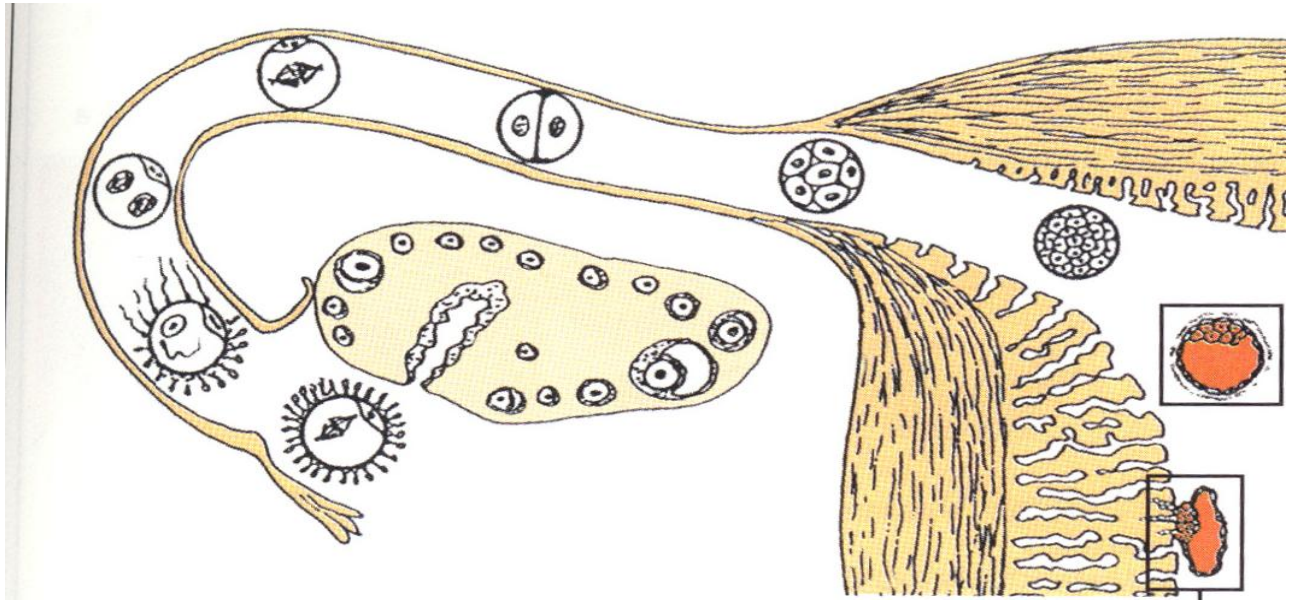
cumulus oophorus


Membrana granulosa
Membrana pellucida
Membrana vitrea
Teca interna

Fecondazione

Esterna, nell'ambiente, es. riccio di mare

Interna, nelle vie genitali femminili, es. uomo

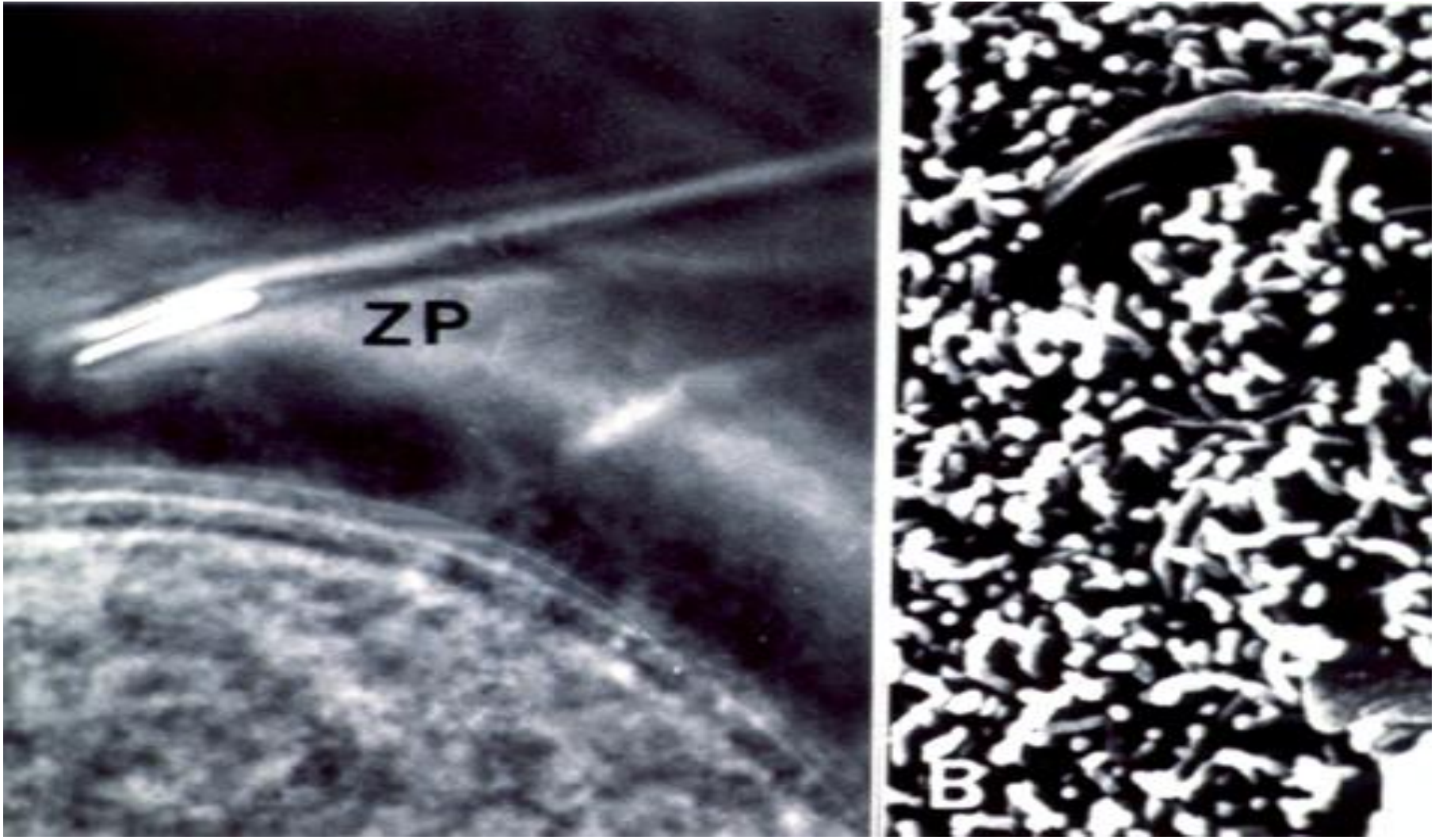


Nel topo:

Ovulati circa 10 oociti

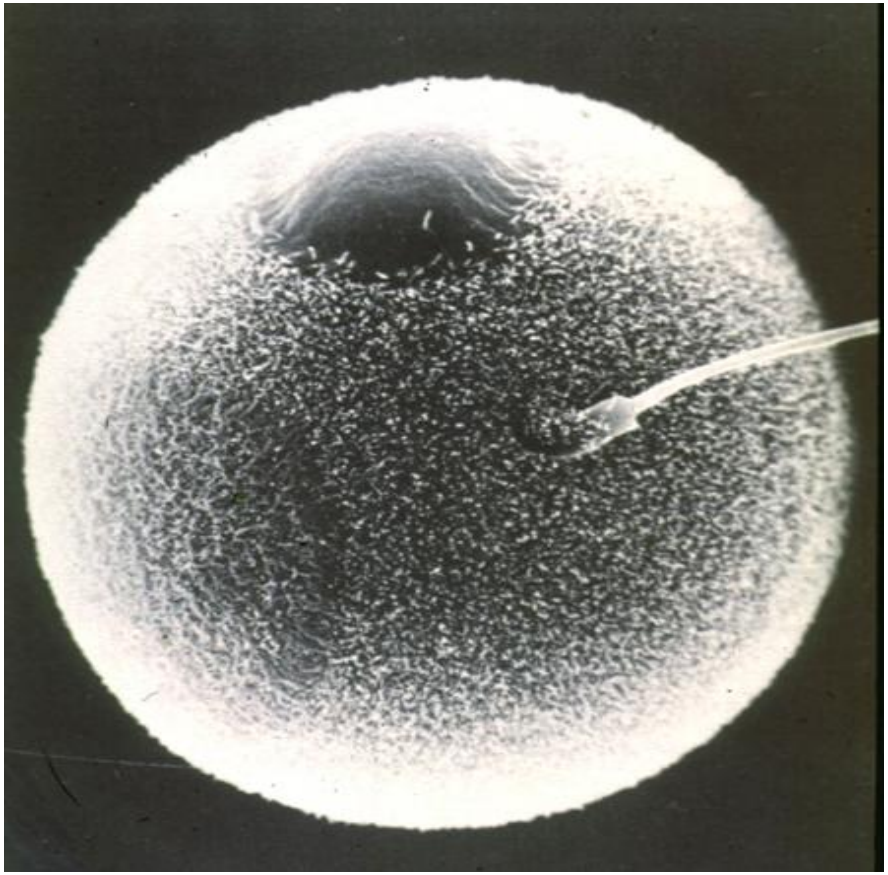
Eiaculati circa 10^7 spermatozoi

Raggiungono l'oocita circa 125 spermatozoi

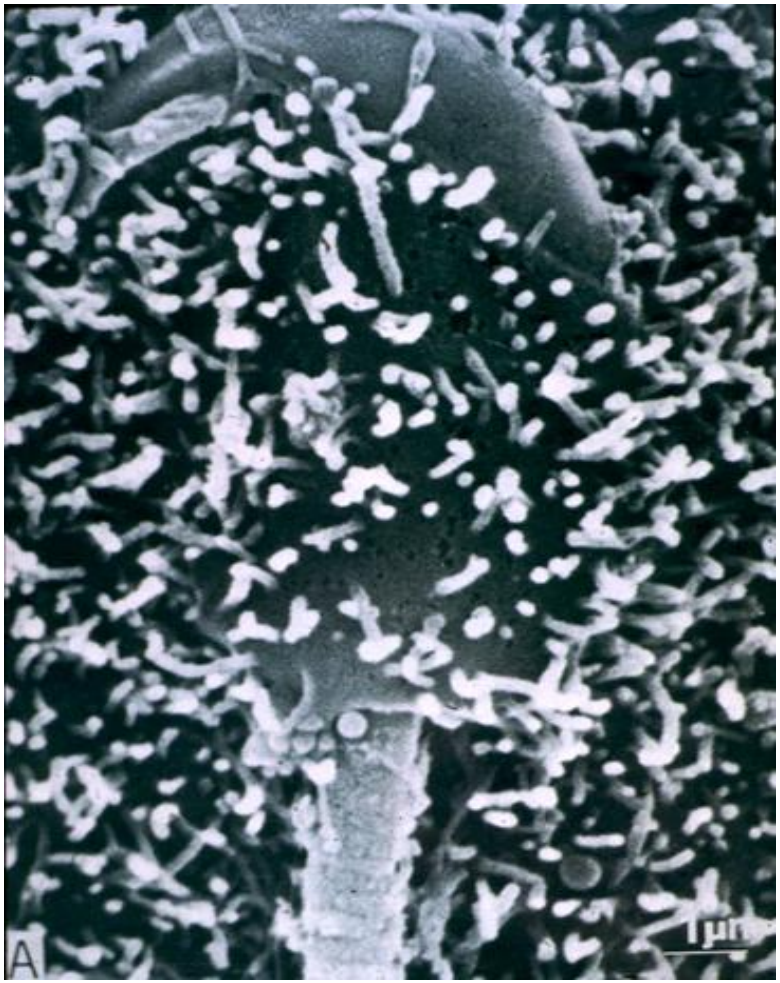


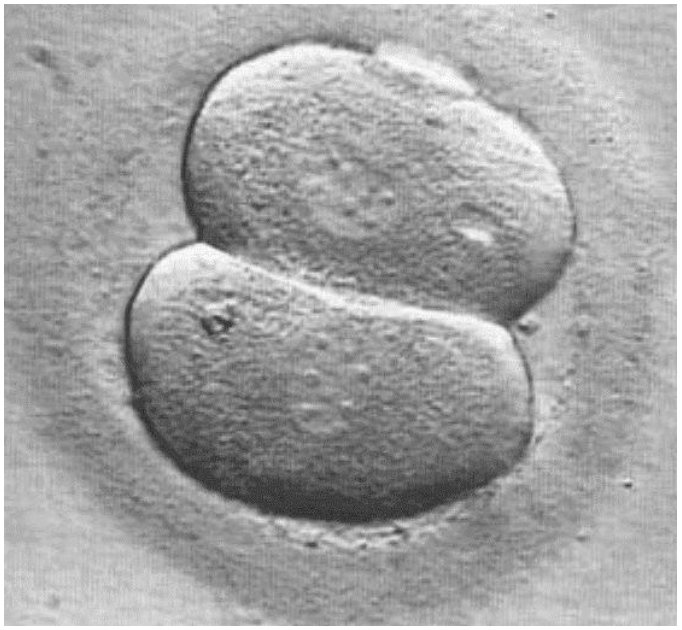
Lo spermatozoo raggiunge la ZP e attraverso la reazione acrosomale penetra fino allo spazio perivitellino per poi fondersi con la membrana plasmatica (oolemma) della cellula uovo

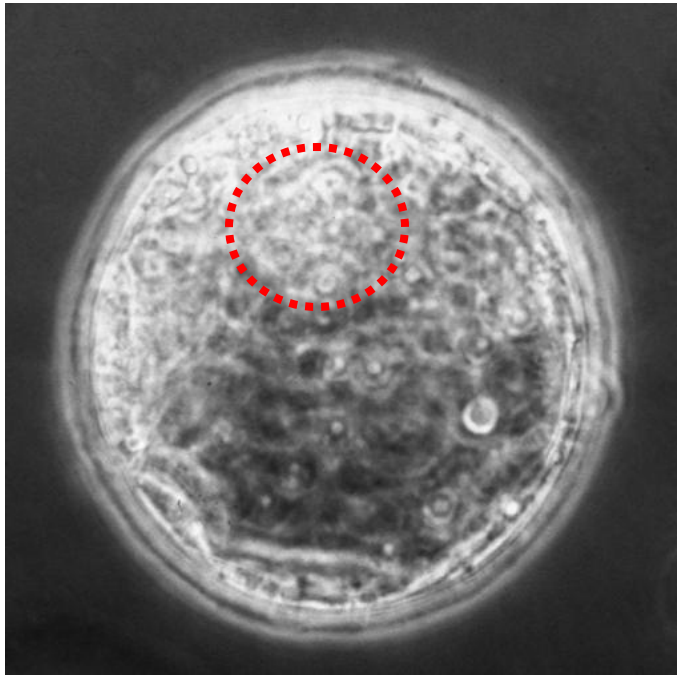
La cellula uovo e' ricoperta da migliaia di microvilli che sono molto importanti nei primi momenti della fusione tra i due gameti. Tutta la superficie esterna della cellula uovo e' ricoperta da microvilli, tranne l'area di espulsione del globulo polare

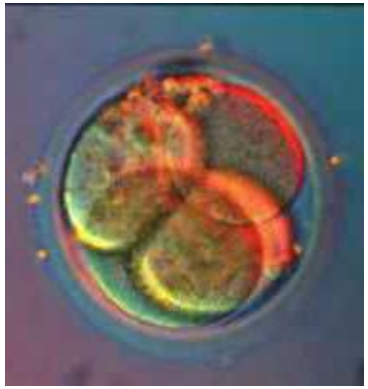


Pochi minuti dopo la fusione tra le membrane plasmatiche dei due gameti, lo spermatozoo penetra all'interno della cellula uovo.









Implantation and Differentiation