Course Instructor

Bruce Hay
haybruce@caltech.edu

Teaching Assistants

Muhammad Abdullah Jauhar
mjauhar@caltech.edu

Emma J. Olinger
eolinger@caltech.edu

Cherise Wong
cherisewong@caltech.edu

Indeever Madireddy
imadired@caltech.edu

Weekly problem sets (lowest score eliminated): 60%
Midterm: 20%
Final: 20%

Recommended Text

An introduction to genetic analysis, A.J.F. Griffiths, et al. 12th edition. W.H. Freeman and Company. ISBN 978-1-319-28646-0.

Chapters 7-9 should be reviewed (skimmed for terms/general sense) if you have not taken Bi 8. If you are unsure of your mastery of the material presented in Bi8, or have come from another department or school and have not taken an equivalent course, read these chapters. For some other parts of the course your book does not provide adequate information, or does so with a slant that is different from what will be presented in class.

Bi 122 - GENETICS
SCHEDULE Version 1.0, 9/20/25 (PRELIMINARY!!!!!)

DATE	LECTURE	LECTURER	PROBLEM SET DUE, TA	READING
9/30	Chromosomes, meiosis	BAH		G, chapters 1-3 Review 7-9.
10/2	Mendel and genes	BAH		G, 2-3, 5
10/7	Sex determination/dosage	BAH	1 ()	G, 1-3
10/9	Quantitative traits, Linkage, and mapping	BAH		G, 4, 19
10/14	Prokaryotes	BAH	2 ()	G, 5
10/16	Mechanisms of recombination	BAH		G, 15
10/21	Rearrangements	BAH	3 ()	G, 17
10/23	Mobile genetic elements	BAH		G, 16
10/28	epigenetics and cloning	BAH	4 ()	G, 12
10/30	extranuclear and prions	BAH	**midterm out 10/ 30**	G, 3
11/4	Gene regulation	BAH	**midterm due 11/4 5PM**	G, 11, 12
11/6	Genomics	BAH		G, 14 ß
11/11	mutation and cancer	BAH		G 13, 15
11/13	genetic screens	BAH	5 ()	G, 13, 15
11/18	Development 1	BAH		G, 13
11/20	Development 2	BAH	6 ()	G, 13
11/25	Population genetics 1	BAH		G, 18, 20
12/2	population genetics 2	BAH	7 ()	G, 18,20
12/4	Immunogenetics	BAH		
			8 () out 12/1, due 12/4	

Final handed out December 9
FINAL DUE BY 5PM, December 12

G, An introduction to genetic analysis, A.J.F. Griffiths, et al. 12th edition. W.H. Freeman and Company. ISBN 978-1-319-28646-0.

Griffiths, Anthony J. F.,Doebley, John,Peichel, Catherine,Wassarman, David A. Introduction to Genetic Analysis. W. H. Freeman. Chapters 7-9 should be reviewed (skimmed for terms/general sense) if you have not taken Bi 8. If you are unsure of your mastery of the material presented in Bi8/9 or have come from another department or school and have not taken an equivalent course, read these chapters. For some other parts of the course your book does not provide adequate information or does so with a slant that is different from what will be presented in class.

Lectures will usually be supplemented with handouts that summarize the information covered in lecture. Nonetheless, because the material presented in class is often not presented in your book, it might not be a bad idea to visit at least a few of the lectures.

Problem sets are in general handed out on Thursday and due by the beginning of the lecture Tuesday.
Lectures are Tuesday and Thursday from 1:00 - 2:30 p.m.
Problem sessions will be announced for the problem sets.

Grades only

Cannot be used for Bil credit

1: an introduction and some odds and ends

1. DNA as the genetic material

2. The nature of the gene

3. Genes have alleles

4. Genes lie on chromosomes.

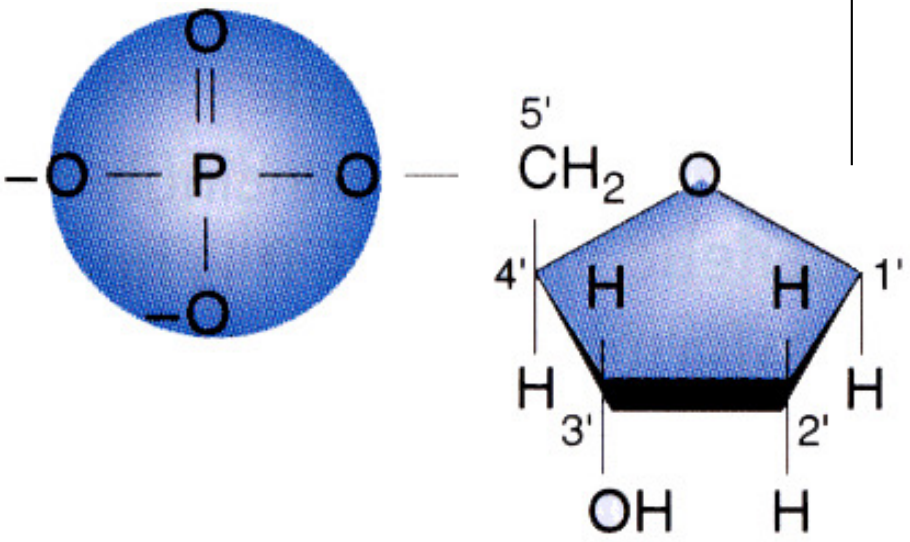
5. Mitosis and Meiosis: Information preservation vs shuffling

6. Polar body diagnosis of disease

7. Beginnings of....Telomeres, aging, cancer, and cloning

Nucleotide

phosphate



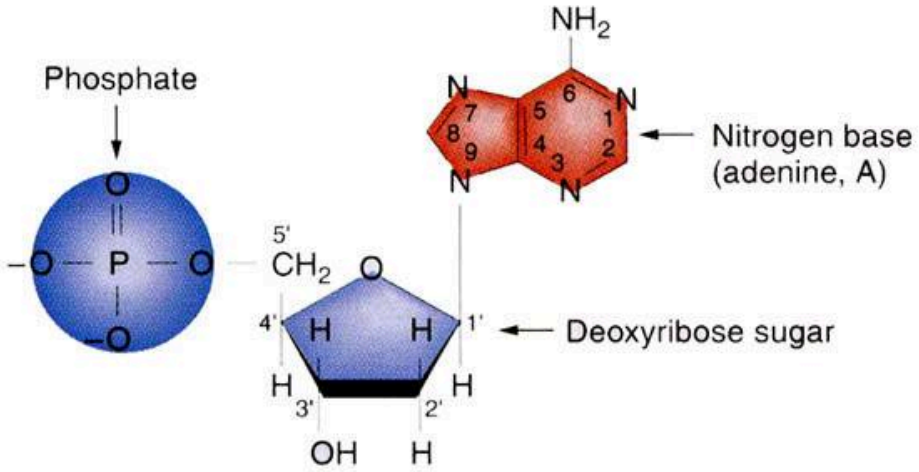
- nitrogenous base:

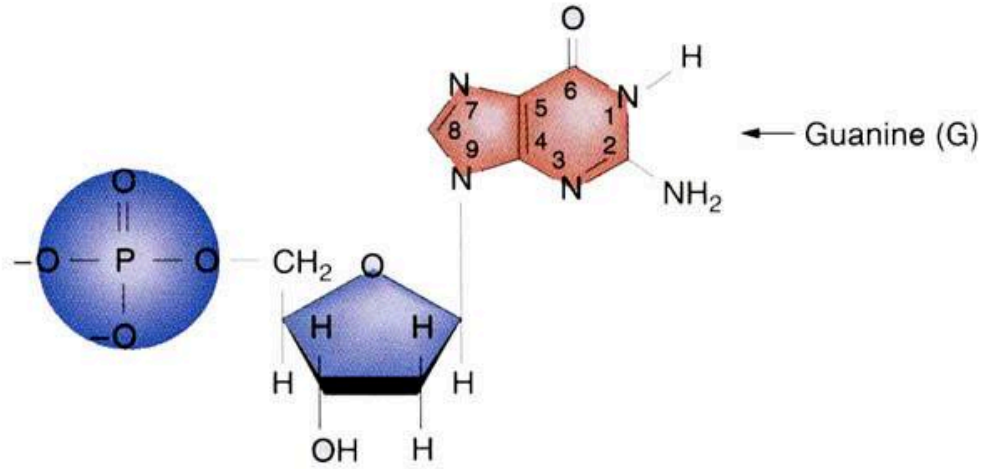
A T G C

pentose sugar

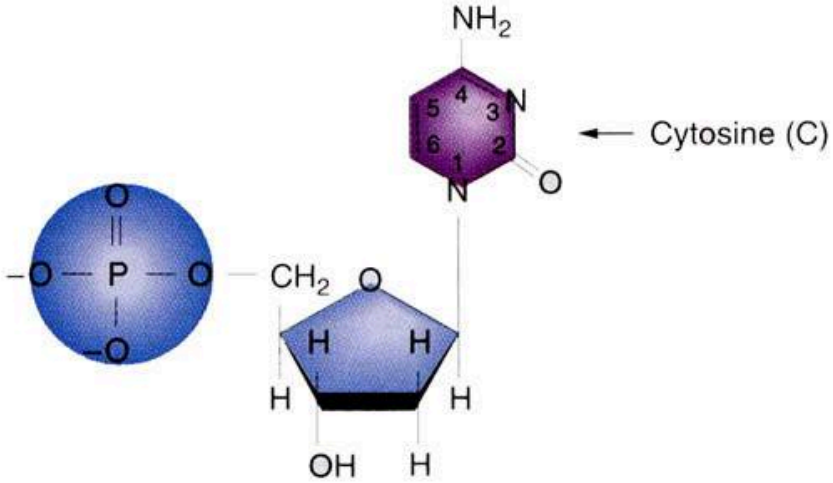
Nucleotides

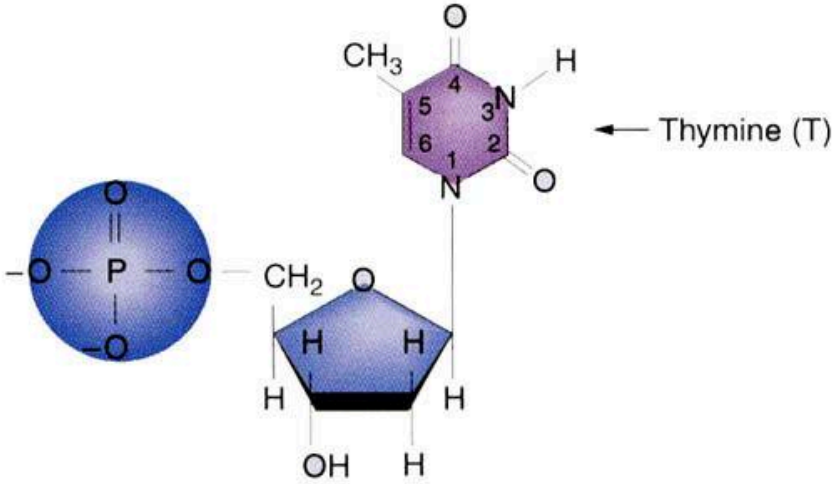
Purine nucleotides





Pyrimidine nucleotides

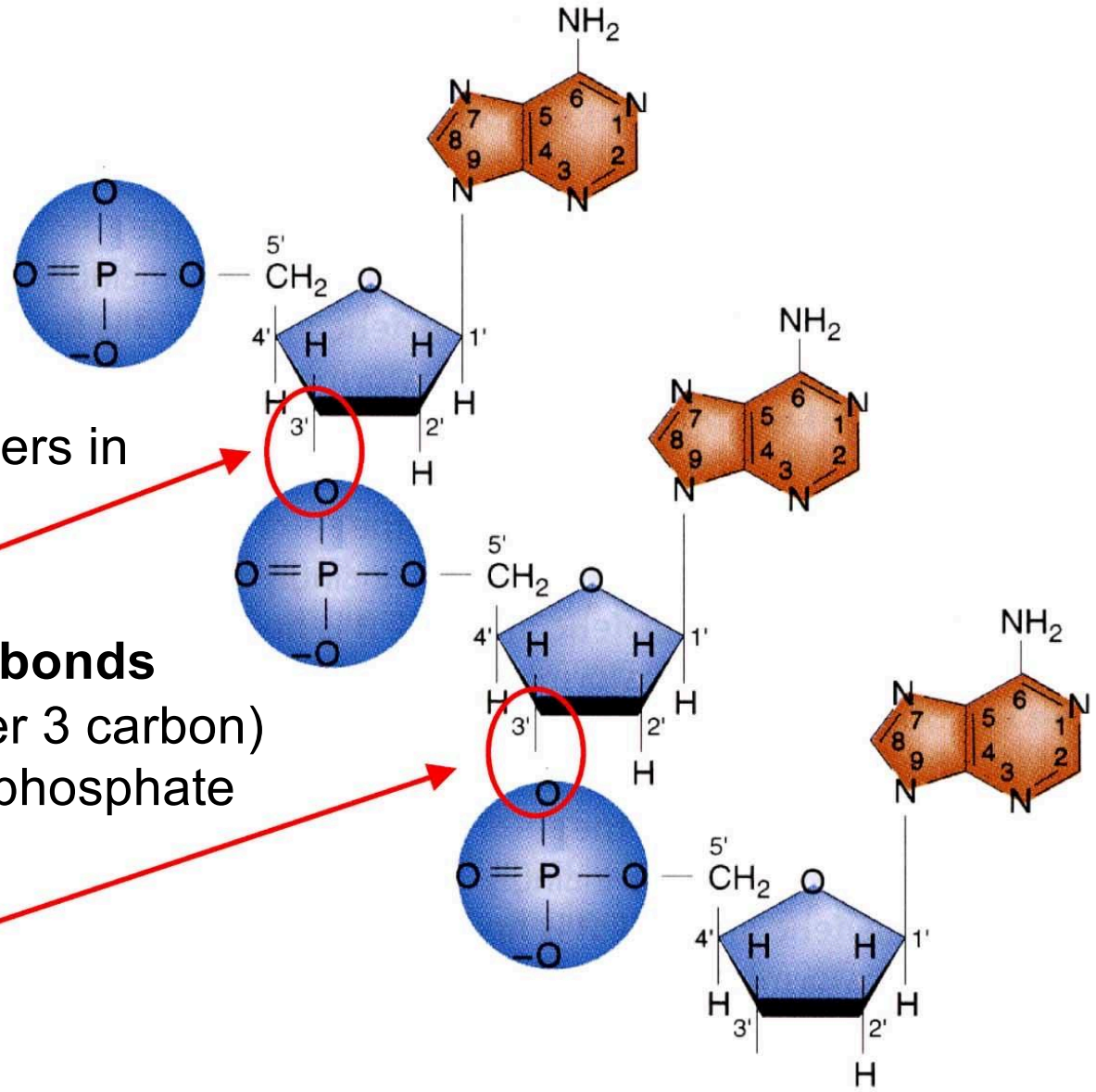




Phosphodiester Bonds

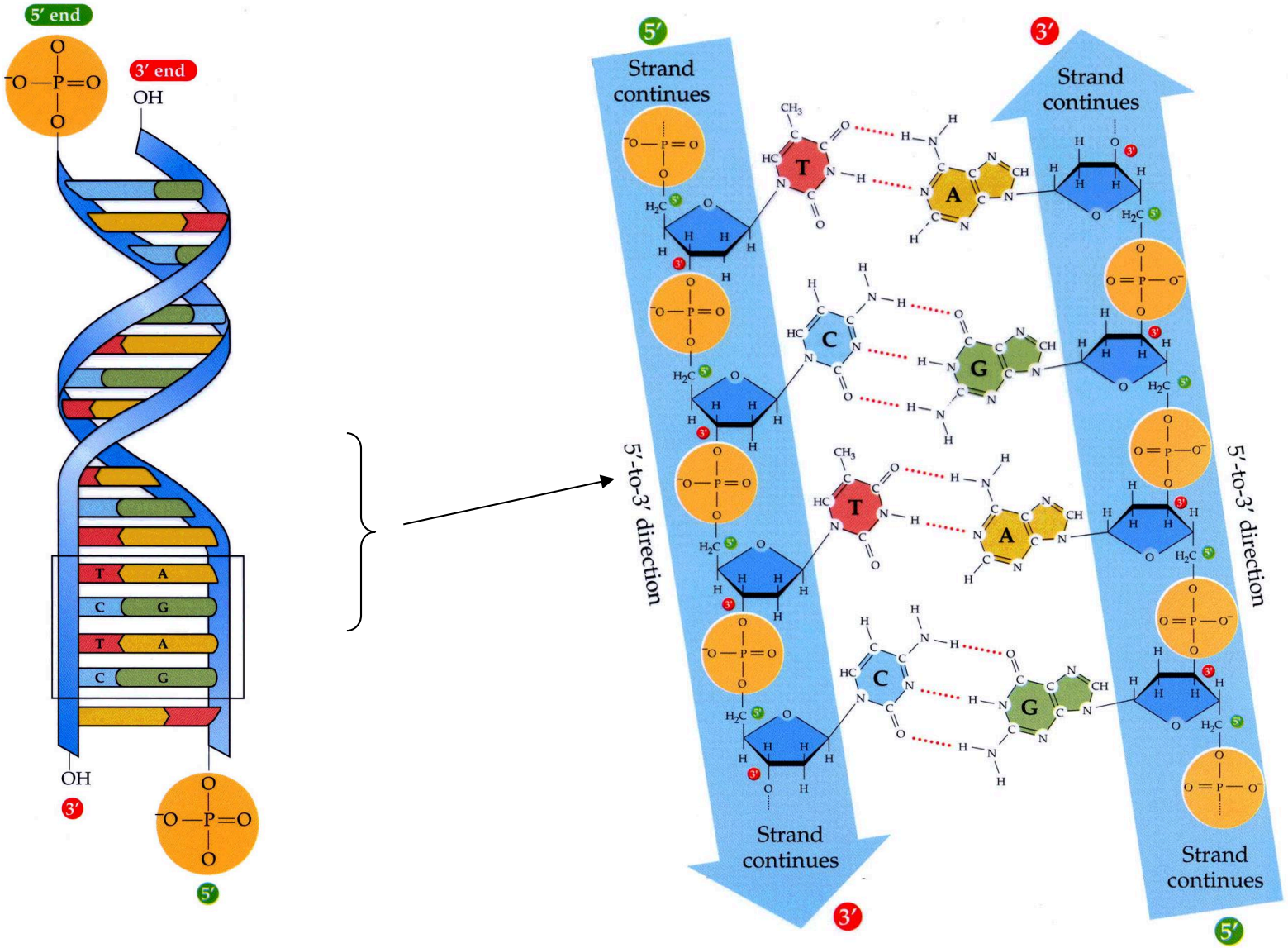
…nucleotides are the monomers in nucleic acids,

…linked by **phosphodiester bonds** between the sugar (number 3 carbon) of one nucleotide and the phosphate of the other.



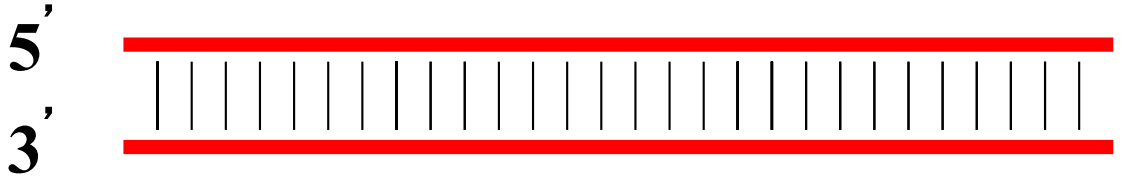
DNA is a double stranded molecule and orients in an anti-parallel fashion,

…orientation is with respect to the phosphodiester bonds.



Hydrogen Bonds

…strands are held together by hydrogen bonds,

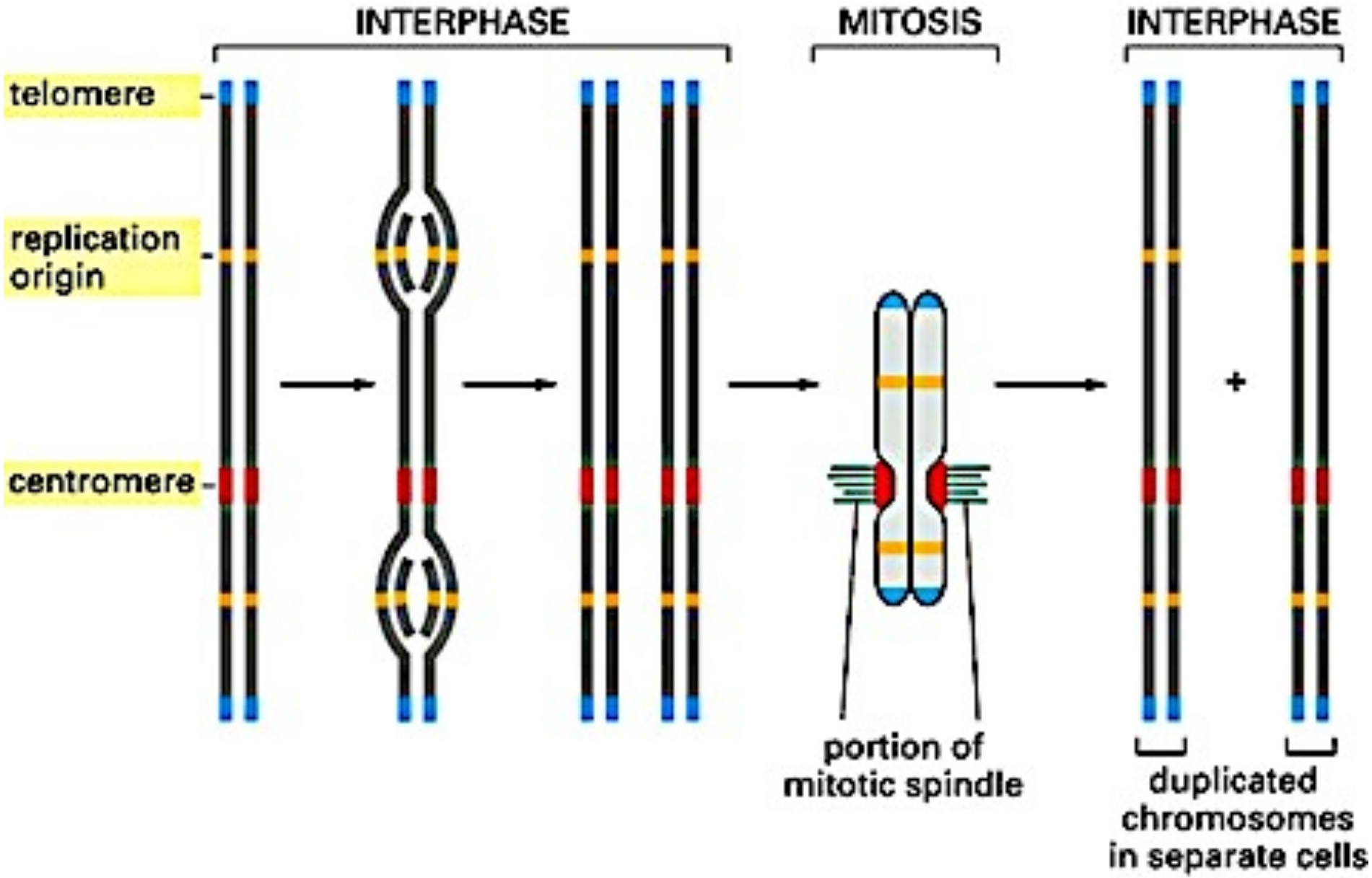


...weak bond, about 3% of covalent bond.

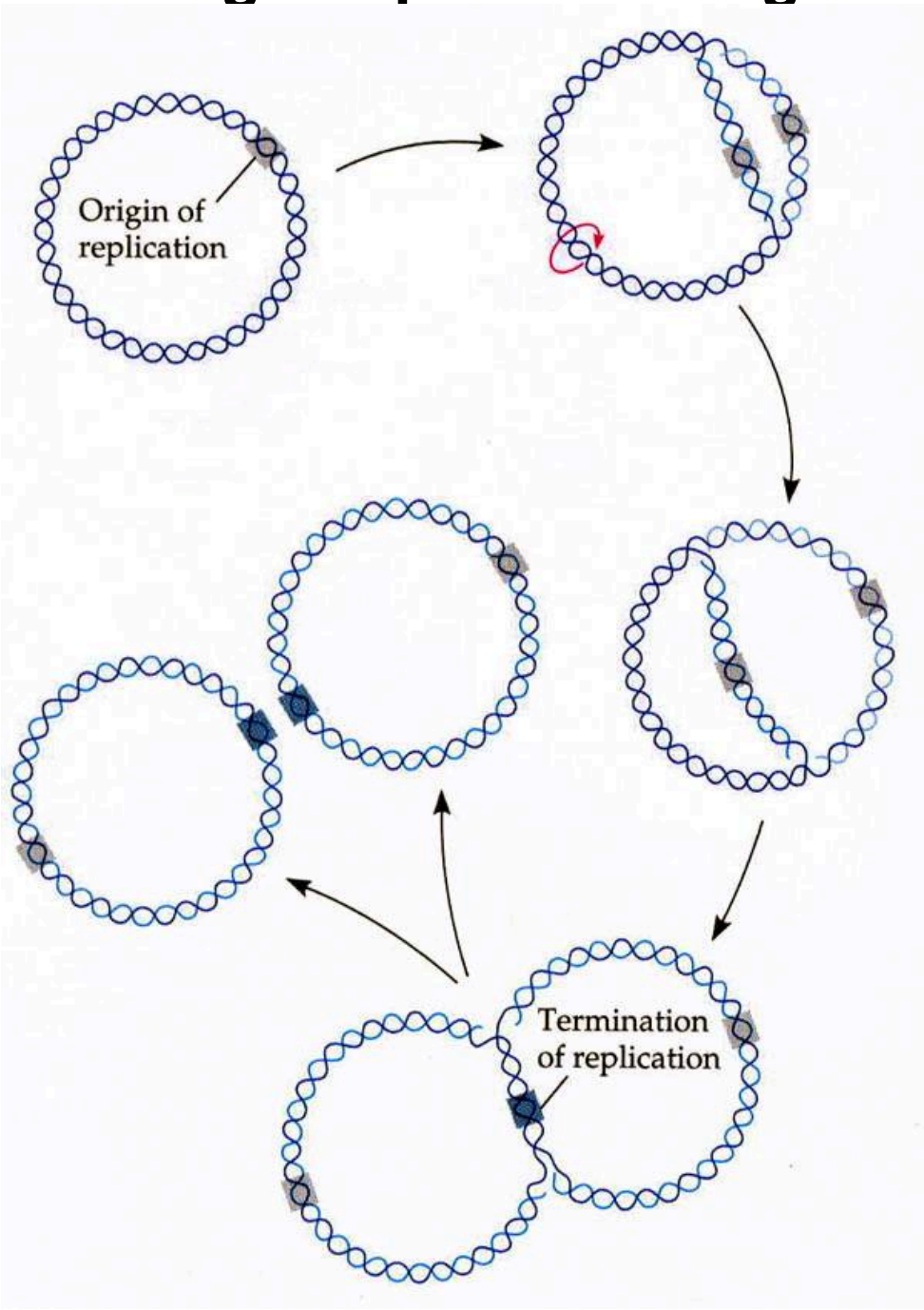
…because the complementary strands of DNA are held together by weak bonds the two strands can be separated using ATP and multi-protein machines

…when separated, the strands can act as templates for replication.

Eukaryotic cells (big linear chromosomes) have multiple replication origins

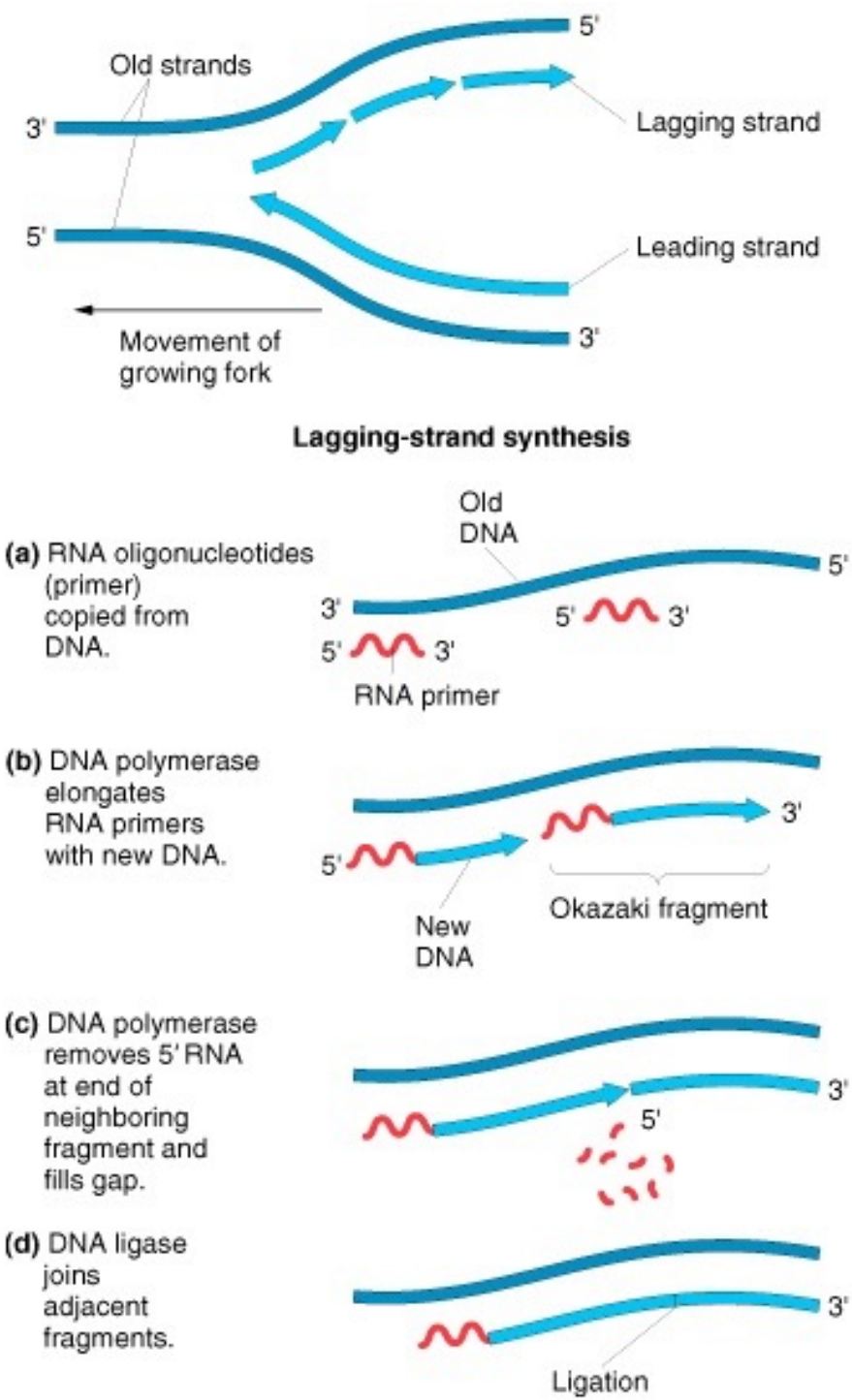


Prokaryotes cells (small circular chromosomes) have a single replication origin



DNA synthesis occurs 5'-3'

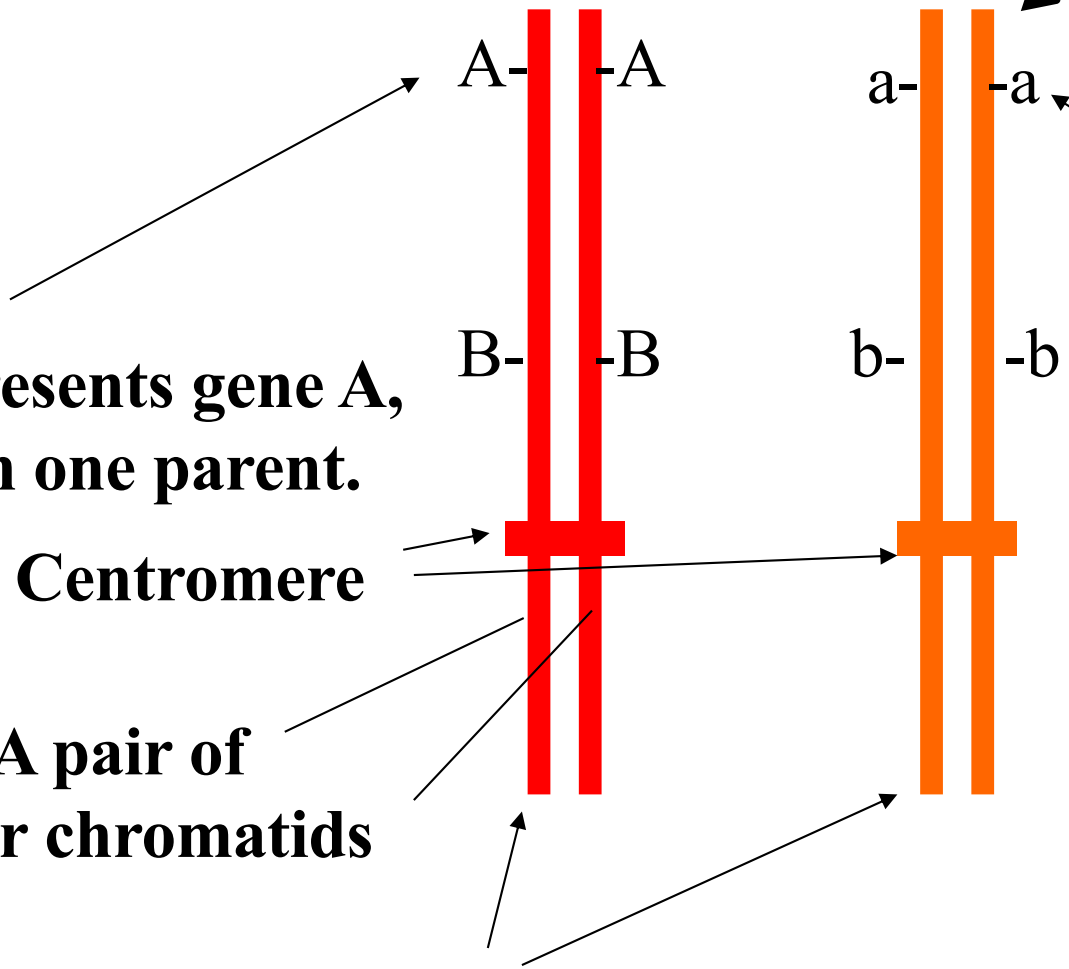
DNA synthesis is initiated using RNA primers, which are ultimately degraded.



Replication

ALLELES = different versions (sequence) of the same gene
haploid = one copy of the chromosome/cell
diploid = two copies of the chromosome/cell

Each line here
Is a double helix



represents gene A, from one parent.

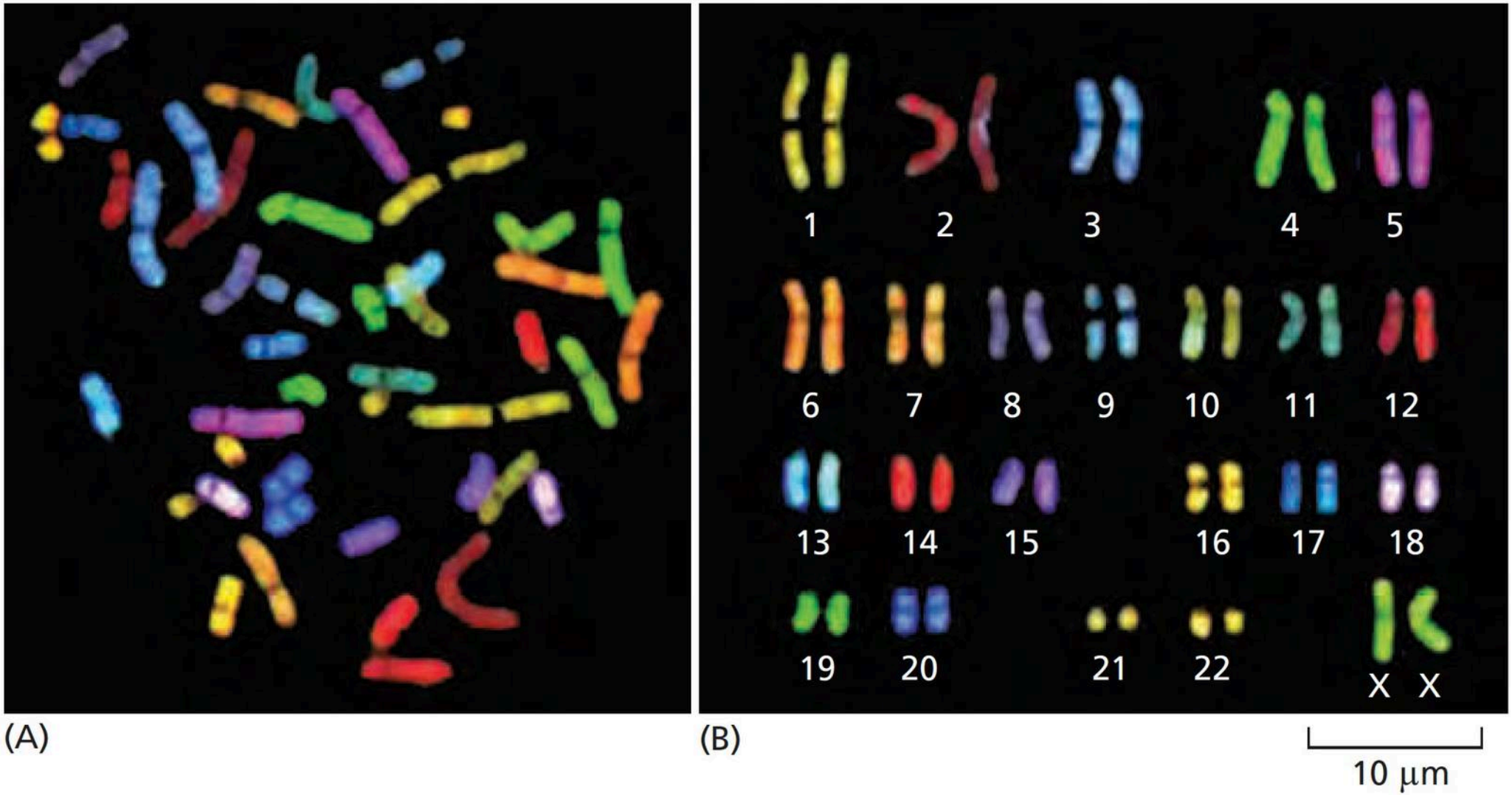
Centromere

A pair of Sister chromatids

Homologous Chromosomes

represents same gene from the other parent, codes for the same protein, may have a slightly different DNA sequence.

Eukaryotes typically have multiple, distinct linear chromosomes



Central Dogma

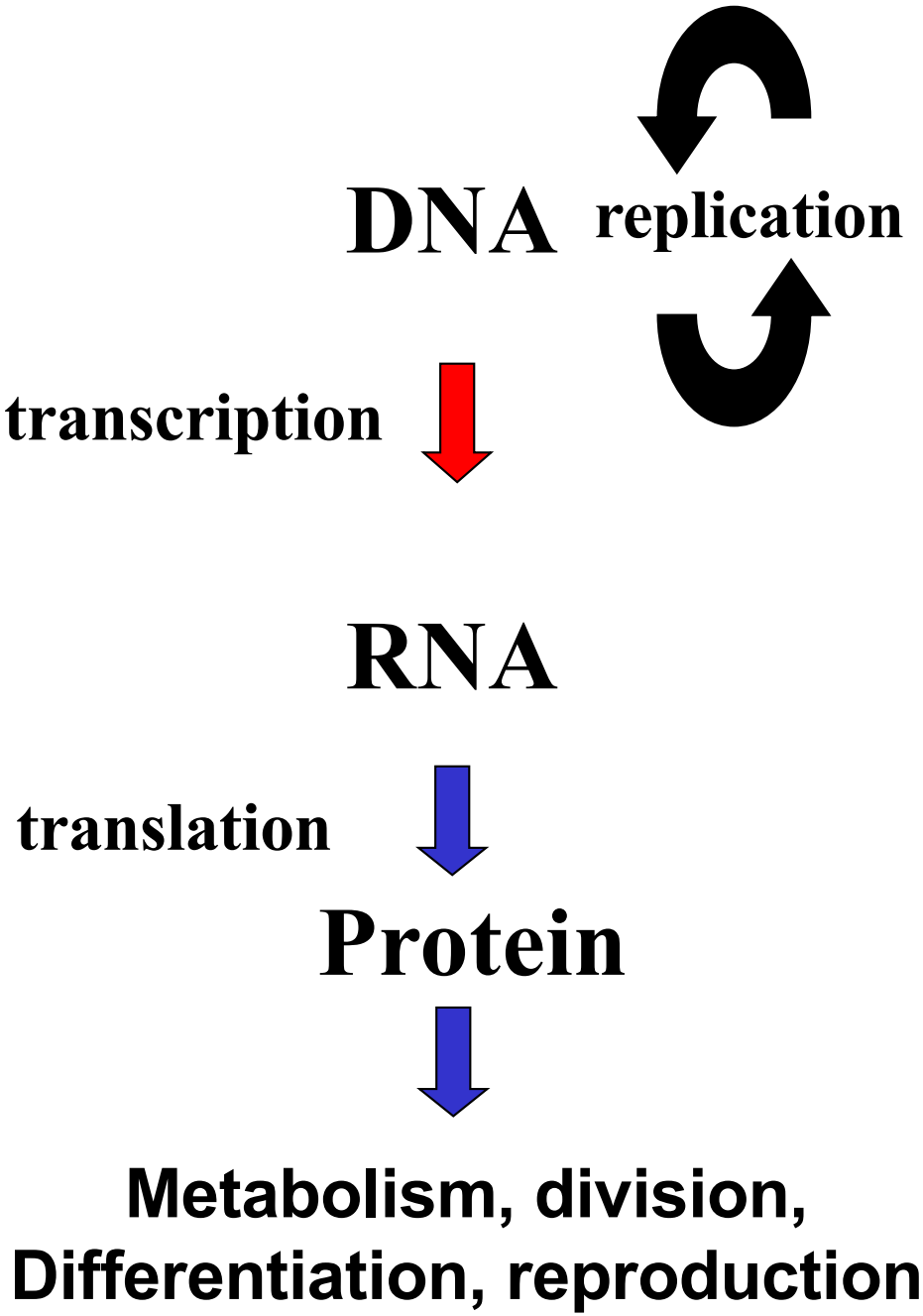
Dogma: Information flows from DNA to RNA to protein. The genome is constant except when mistakes are made.

Incomplete!!!!

Many new observations show that information flows from proteins to RNA and to DNA, and from RNA to DNA

Genomes engage in active modification

In other words, your genome is often subject to modification from the environment. And this can be adaptive.

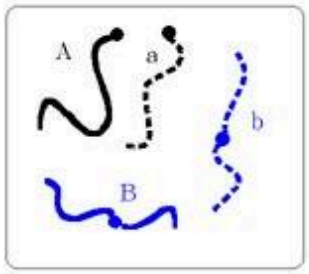


MITOTIC CYCLE (high fidelity creation of identical clones)

INTERHPASE

Diploid cell = 2n
Haploid cell = 1n

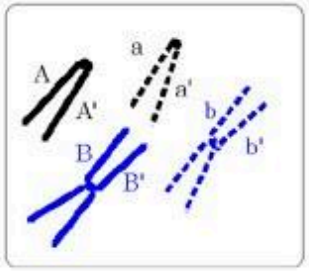
n = # of basic chromosome types
= 2 (A/a type, B/b type)

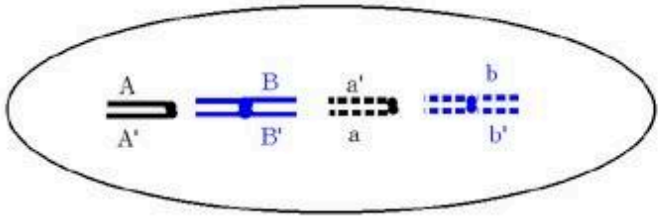


S PHASE

DNA REPLICATION

PROPHASE





METAPHASE

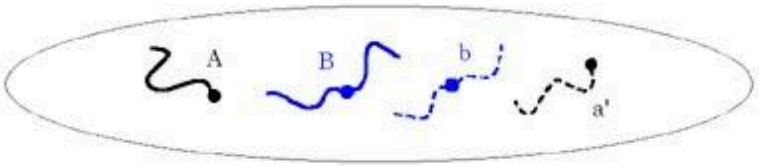
Sister chromatids align
Homologs do not pair

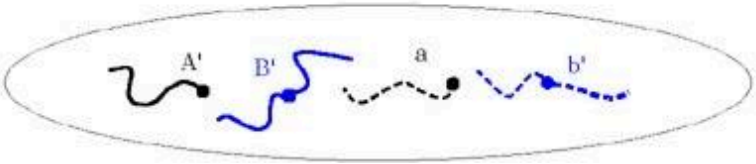
Sister chromatids disjoin

ANAPHASE

Cytokinesis

TELOPHASE

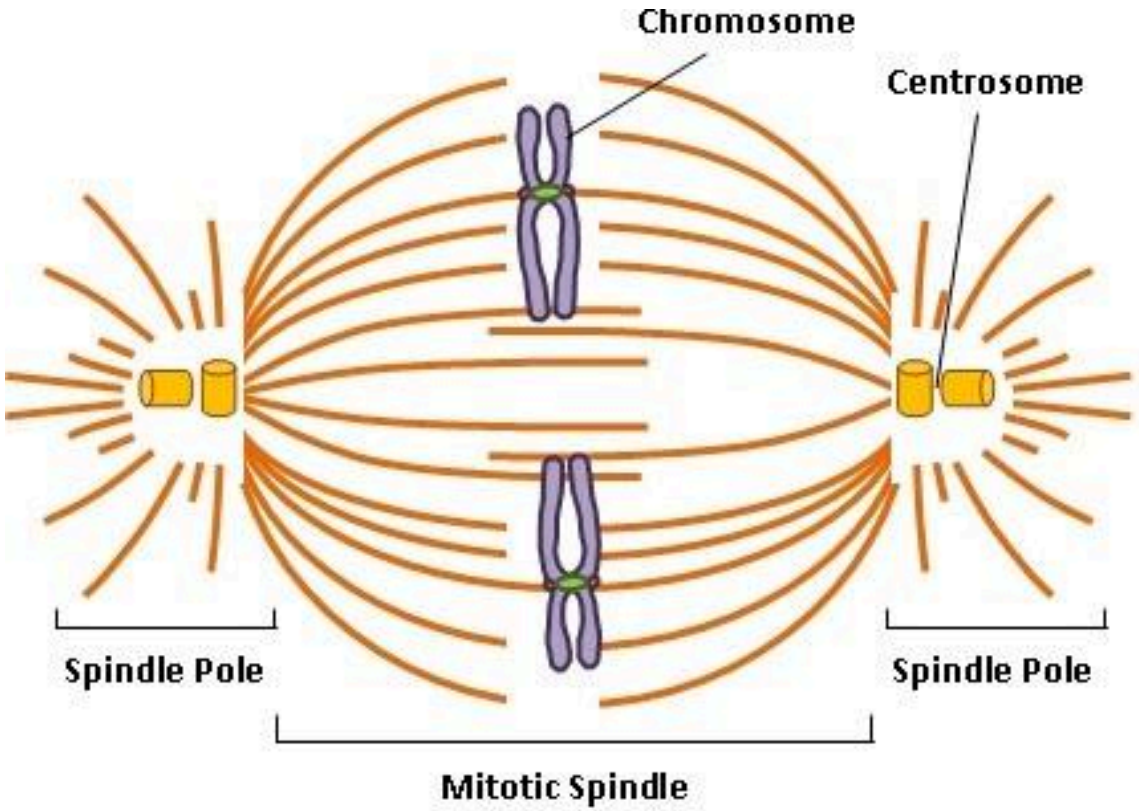




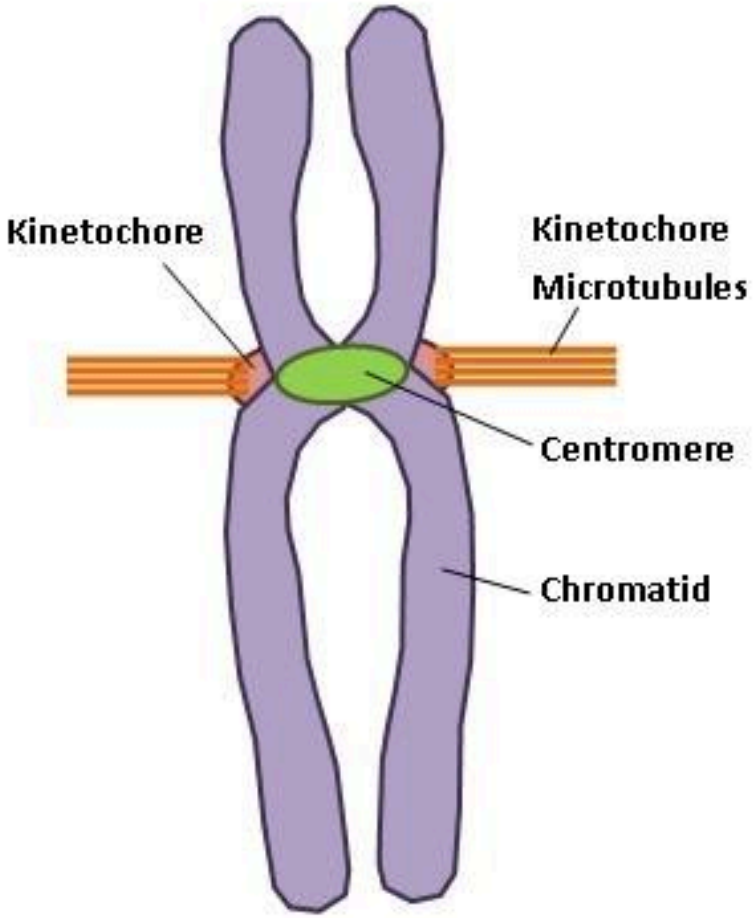
Mitosis generates clones of cells

IDENTICAL DAUGHTER CELLS

Chromosome segregation, the kinetochore and centromere



Mitotic Spindle at Metaphase



Detail of Chromosome

Sexual reproduction, meiosis, and the creation of genetic diversity

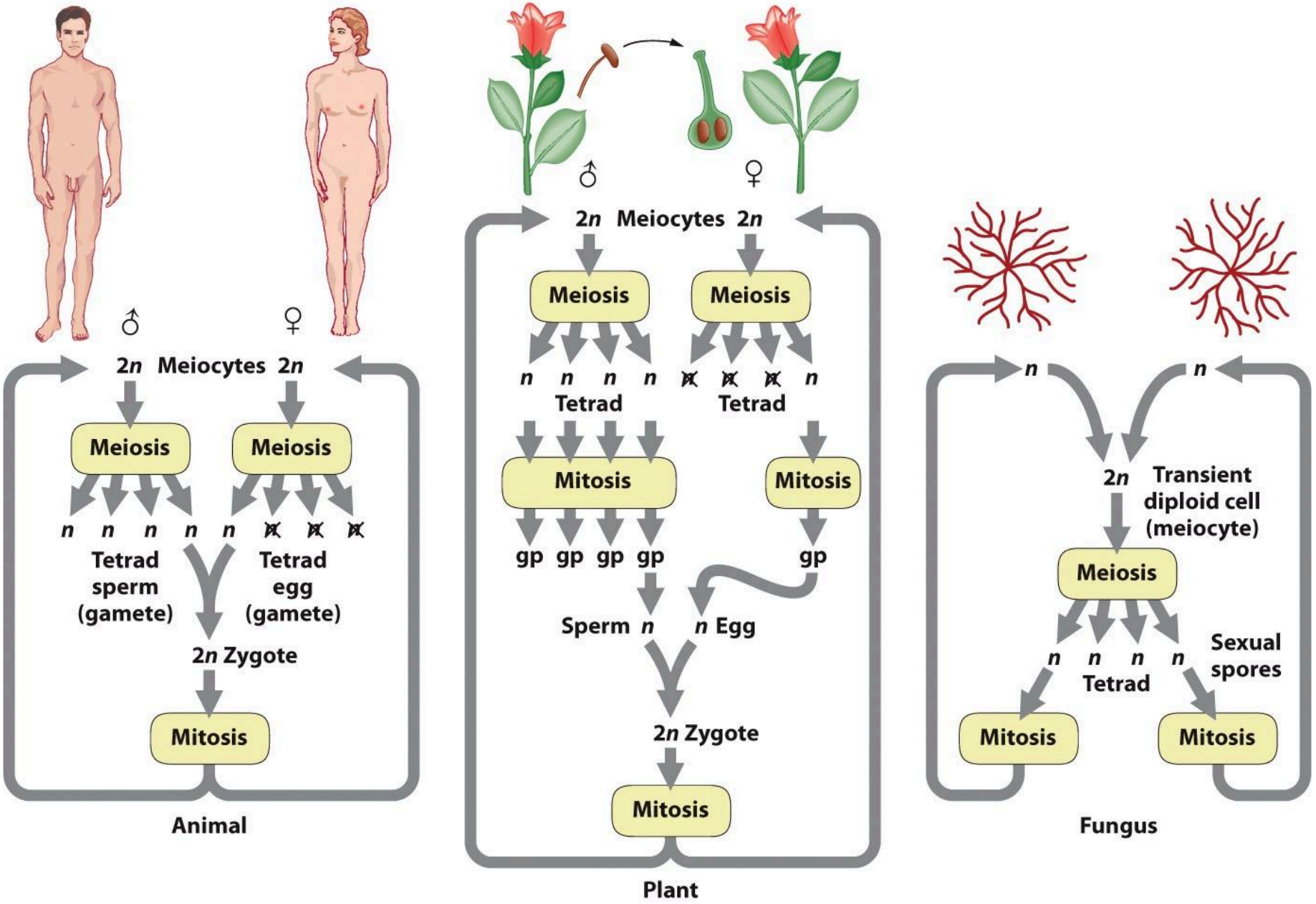
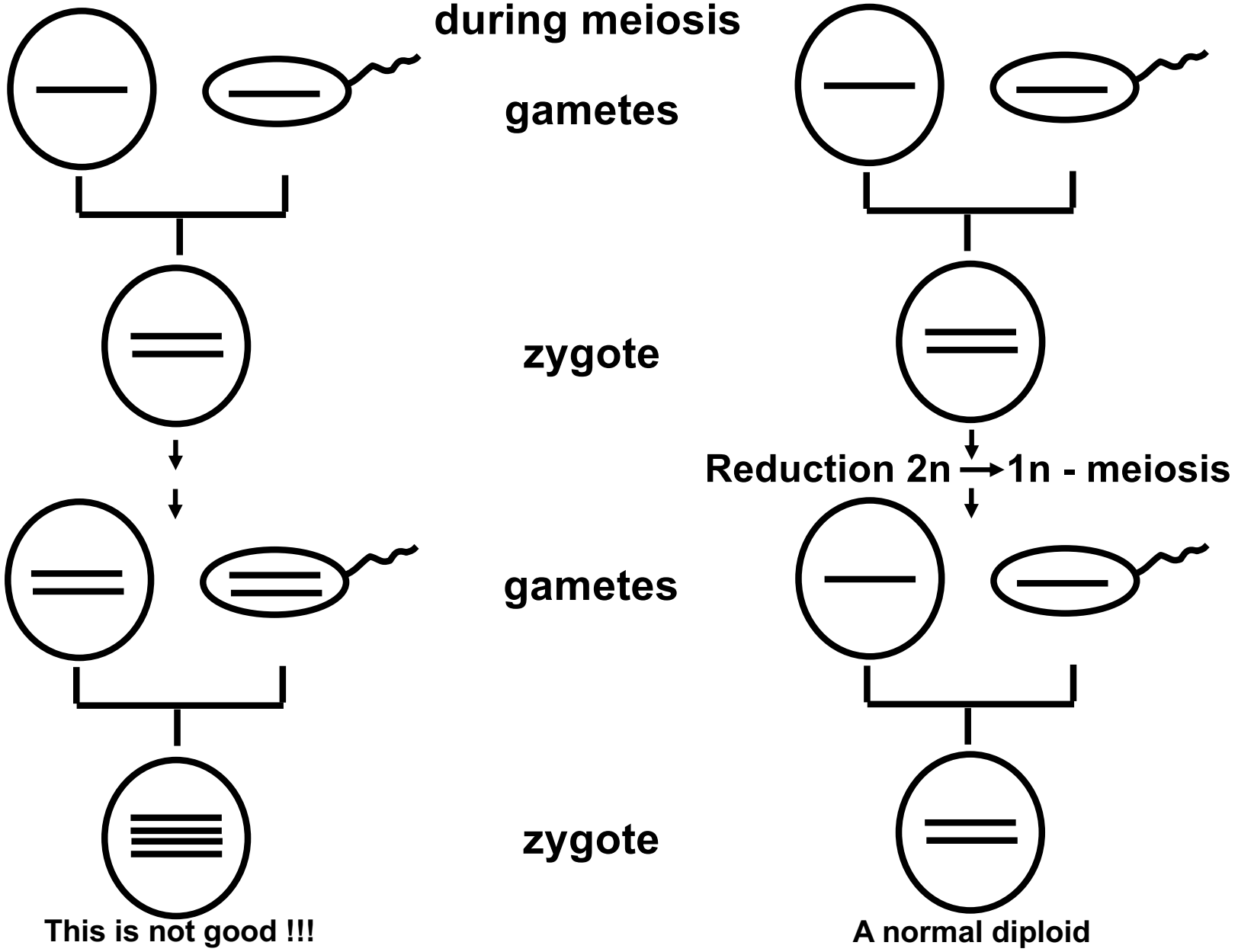


Figure 2-6
Introduction to Genetic Analysis, Twelfth Edition

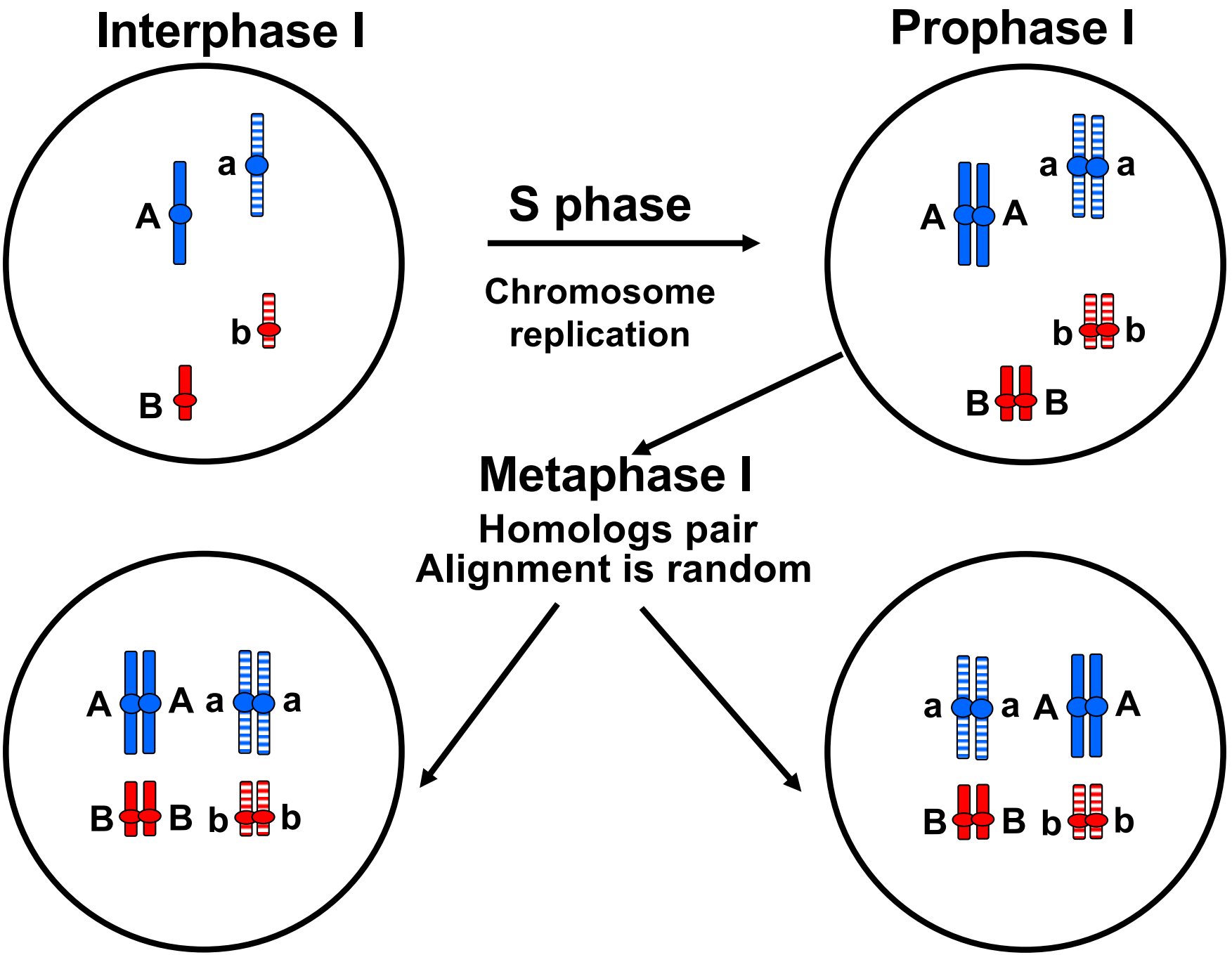
Sexual reproduction - The need for a reductive division during meiosis



One set of chromosomes (1n), haploid

Two sets of chromosomes (2n), diploid

Meiotic cycle--the beginning



MITOTIC CYCLE

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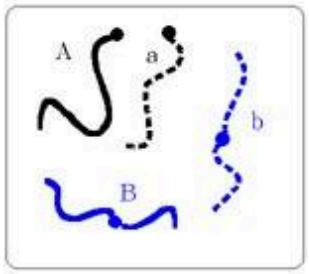
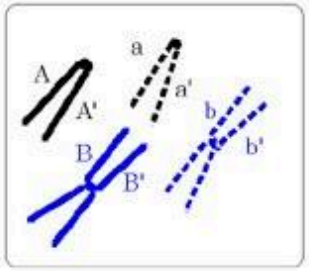
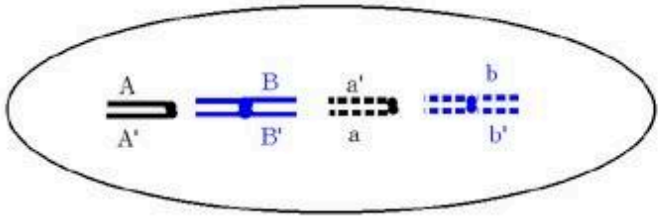


S PHASE

DNA REPLICATION

PROPHASE





METAPHASE

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ANAPHASE

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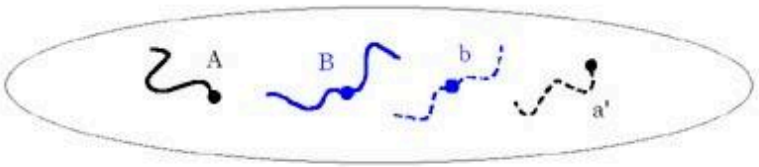
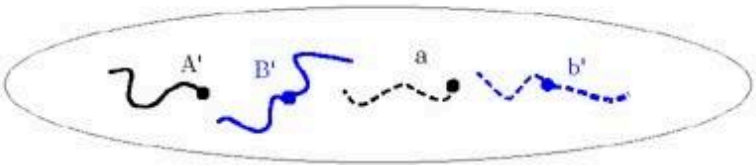
TELOPHASE



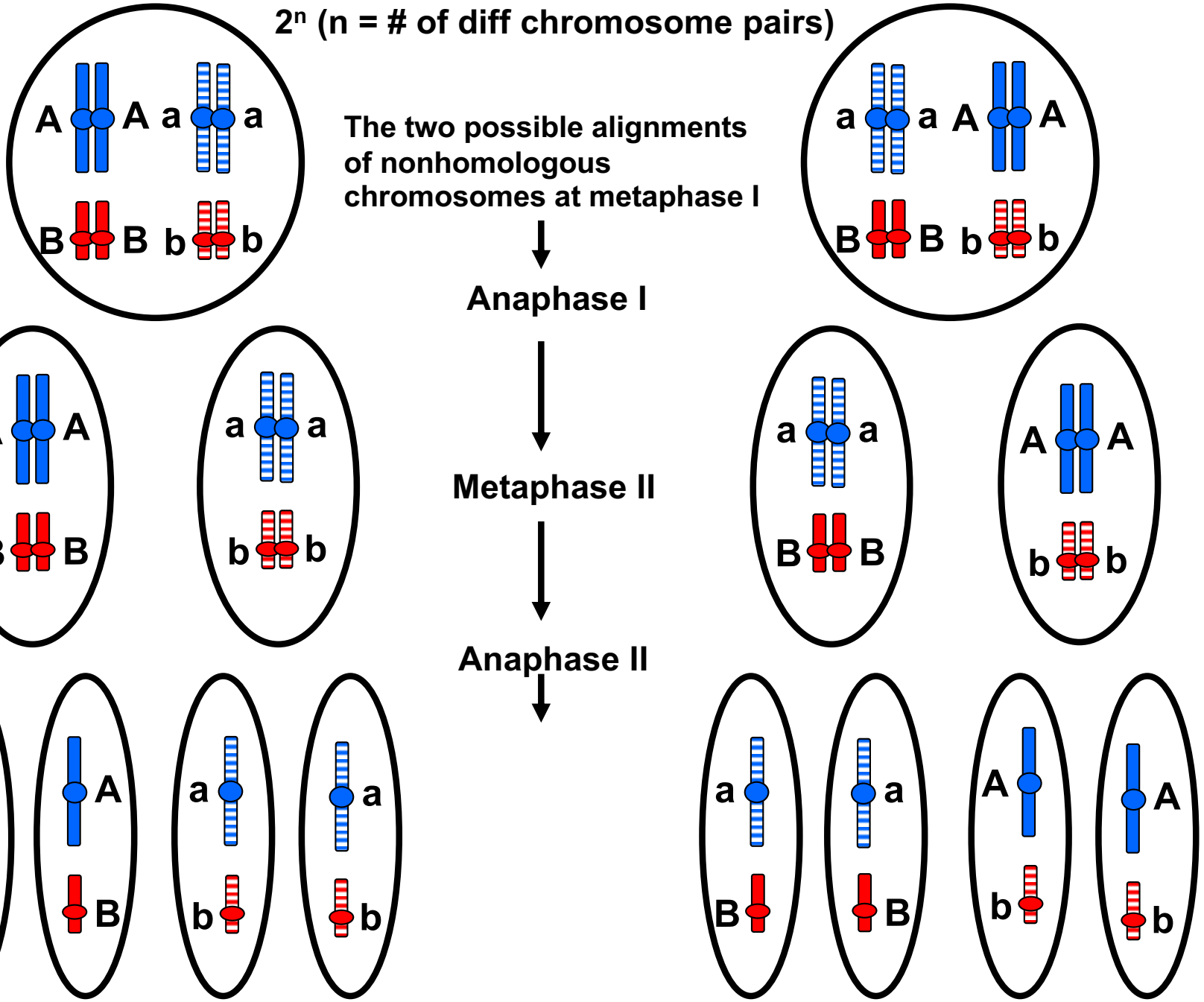


Mitosis generates clones of cells

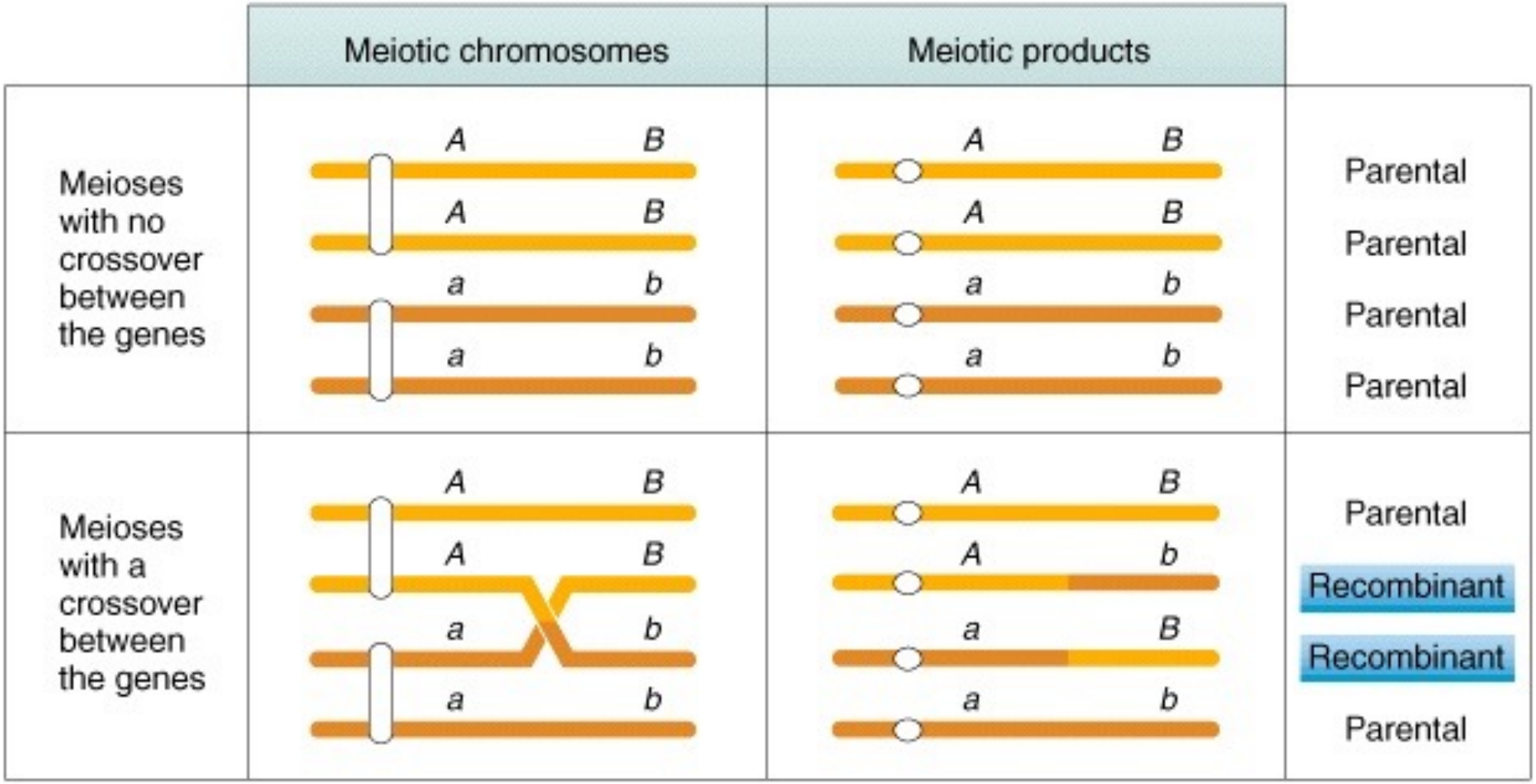
IDENTICAL DAUGHTER CELLS

Meiosis without recombination. Independent assortment of homologs to different Poles creates gamete diversity

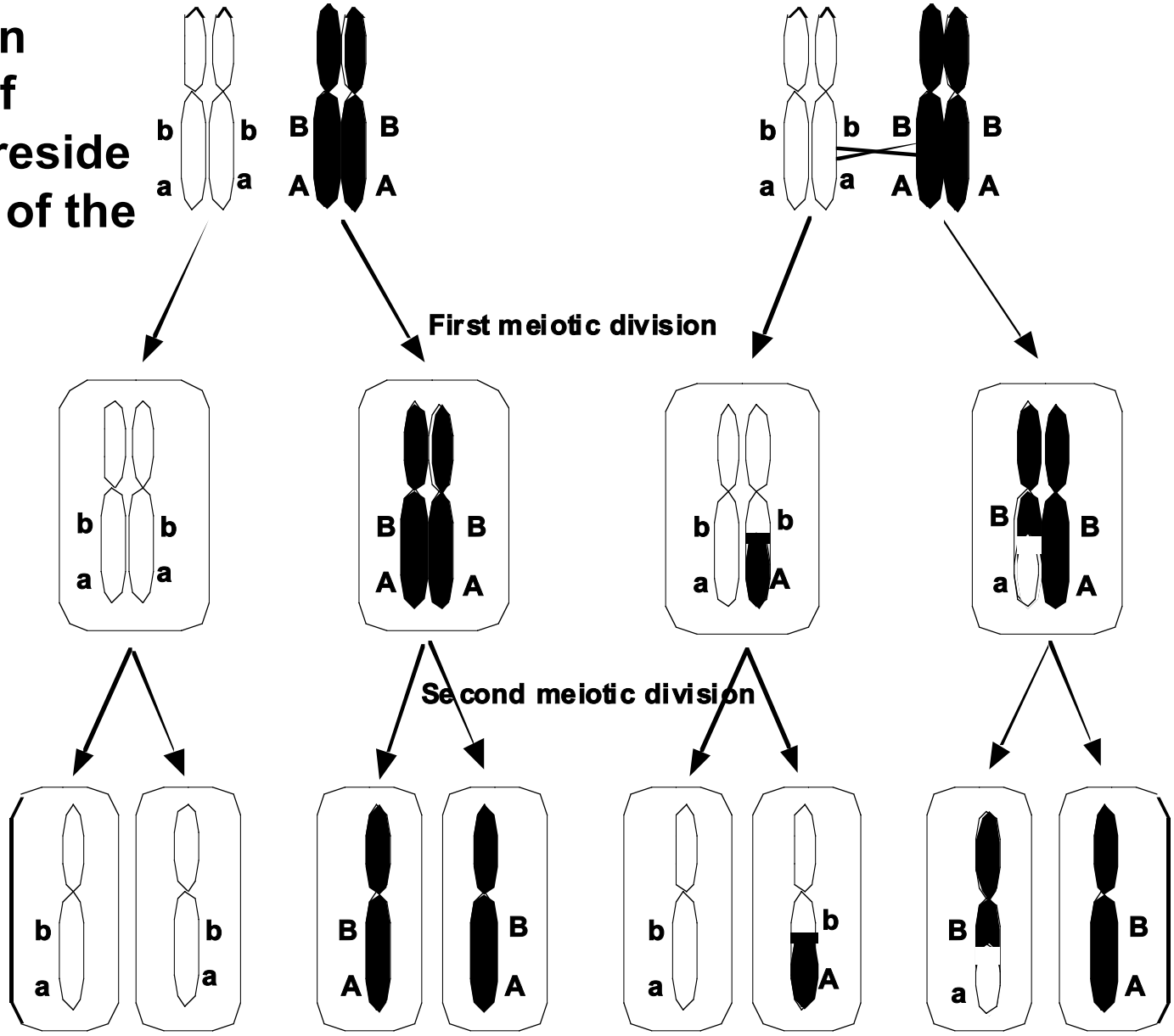
2^n (n = # of diff chromosome pairs)



MEIOTIC RECOMBINATION: SHUFFLING OF DNA BETWEEN HOMOLOGOUS CHROMOSOMES



Meiotic recombination allows for shuffling of alleles of genes that reside on different versions of the same homologous chromosome



Segregation of A-a at the first meiotic division

1. Segregation of A-a at the second meiotic division
2. New gamete combinations of the A and B genes

Sex utilizes two powerful mechanisms to create genetic diversity in progeny

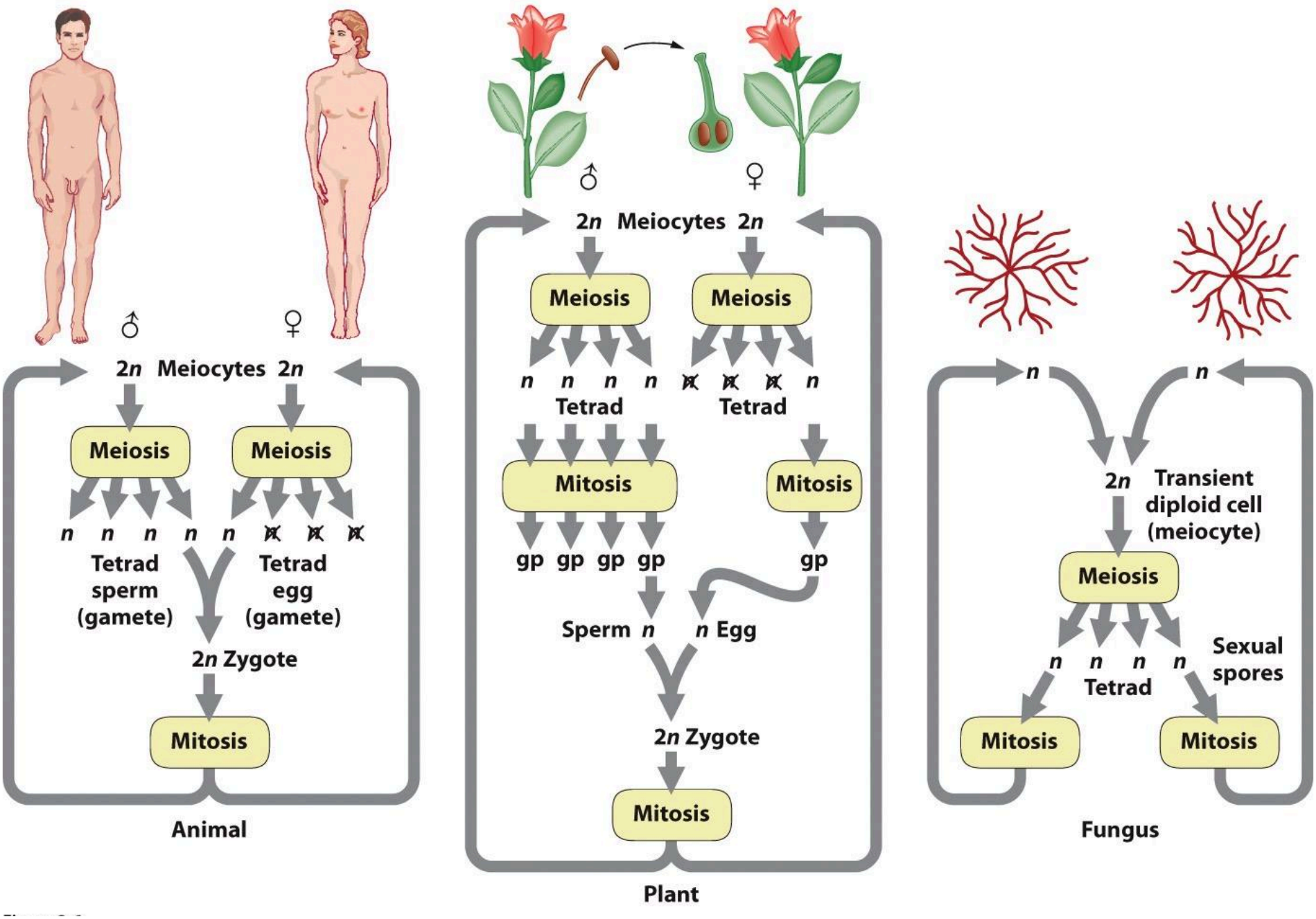
Independent segregation of homologous chromosomes during meiosis 1. Possible gamete types = 2^n, where n = # of chromosome types

Recombination between homologous chromosomes results in shuffling of alleles of genes on the same chromosome from one homolog to the other

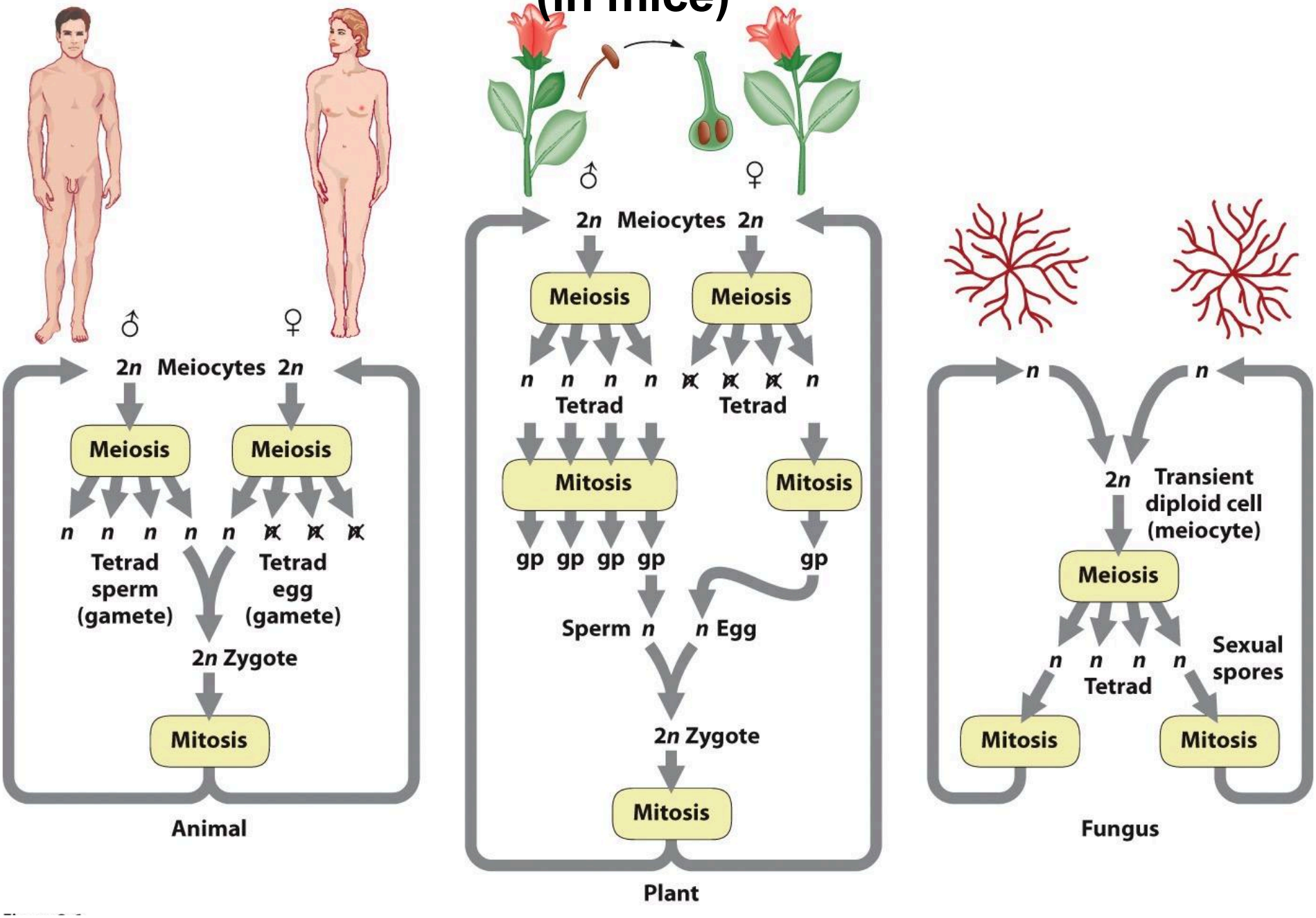
It is extraordinarily unlikely that two offspring of a pair of parents, resulting from independent fertilizations, will be genetically identical.....

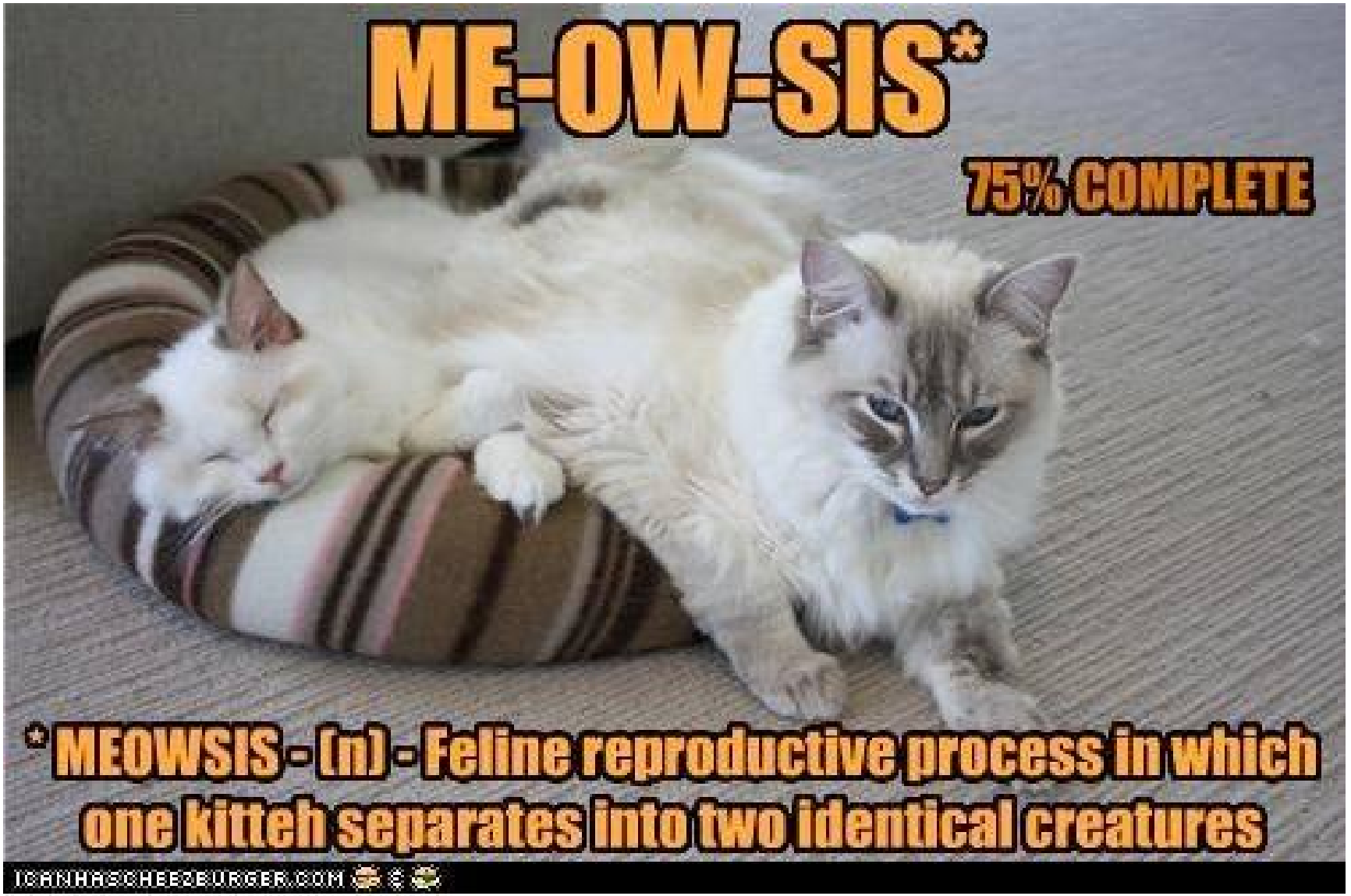
(....but you could still be a clone)

Sexual reproduction, meiosis, and the creation of genetic diversity

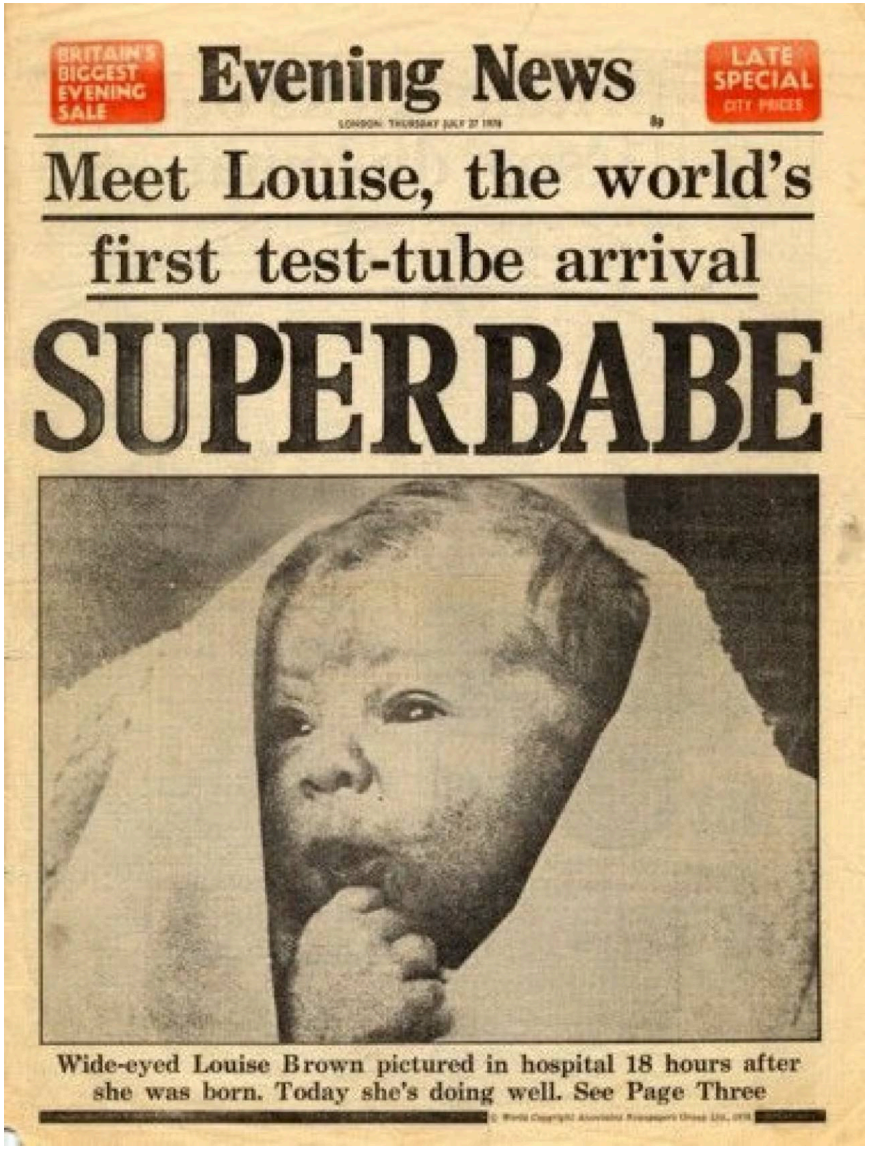


But note.....new developments now allow creation of sperm-sperm progeny and egg-only progeny (in mice)




ME-OW-SIS*
75% COMPLETE
*MEOWSIS - (n) - Feline reproductive process in which one kitteh separates into two identical creatures
ICANHASCHEEZBURGER.COM

Patrick Steptoe, a surgeon; Robert Edwards, a physiologist; and Jean Purdy, a nurse and embryologist



~ 17 million worldwide

Health / Articles

How many IVF babies are born in the US?

One out of every 37 babies born in the US in 2022 was conceived using IVF or other assisted reproductive technology.

Updated August 4, 2025 by the USAFacts team

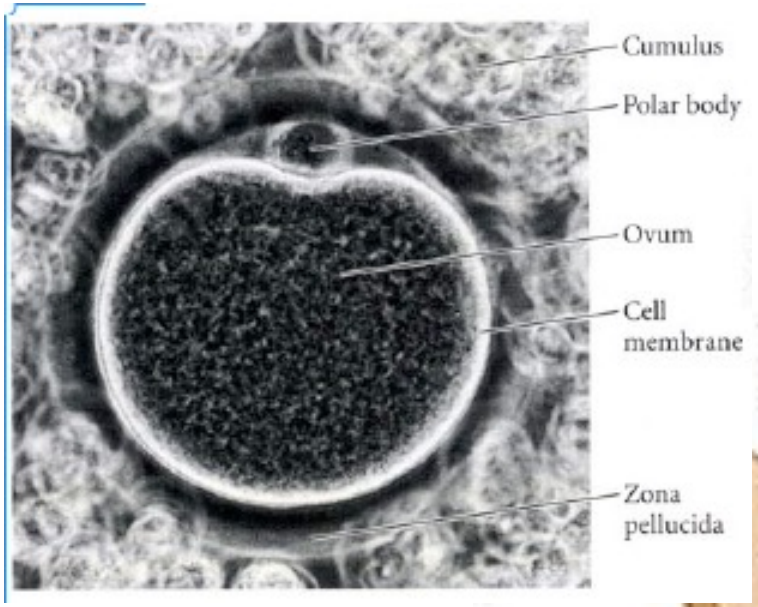
Alabama Rules Frozen Embryos Are Children, Raising Questions About Fertility Care

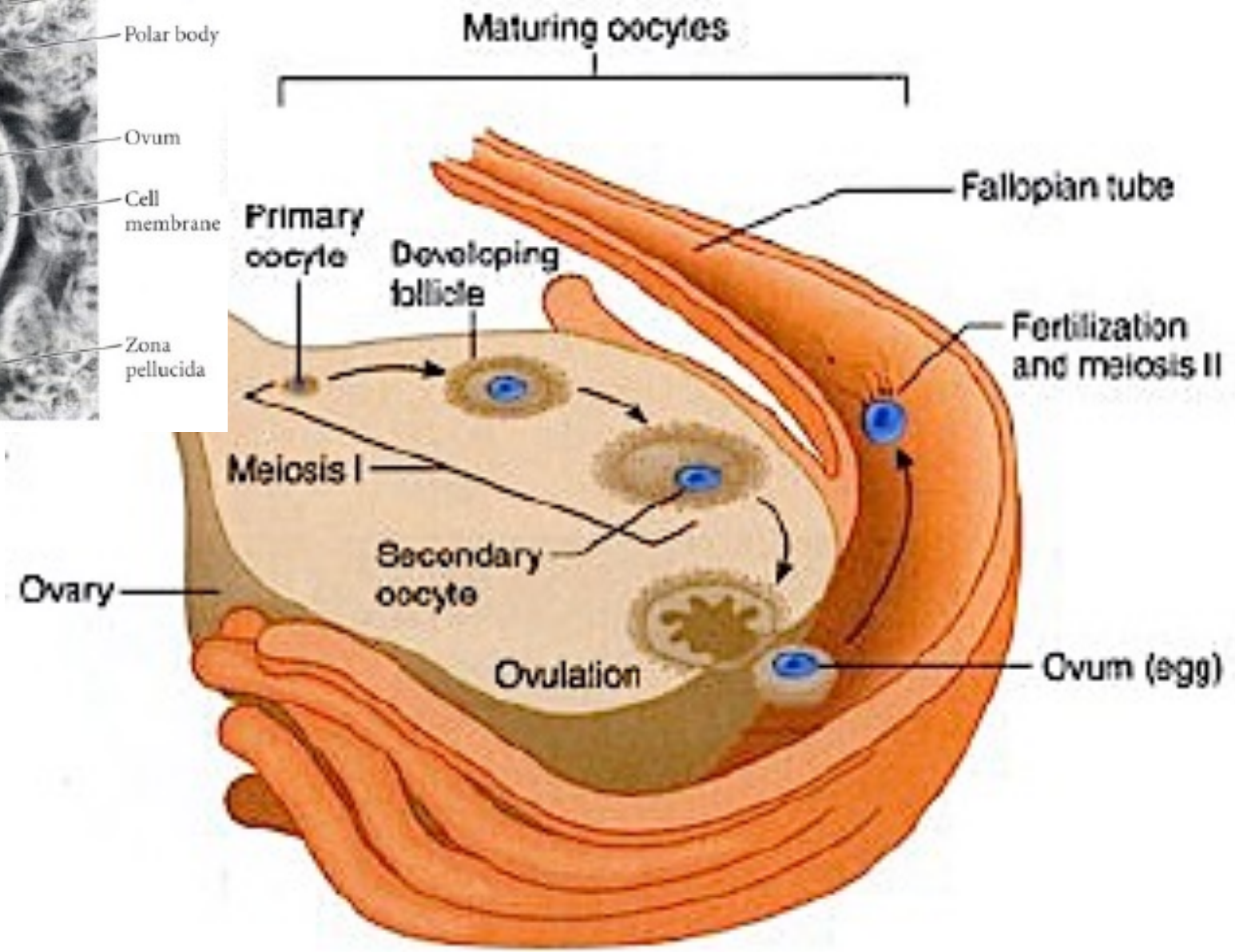
The ruling raises worrisome legal issues for would-be parents far beyond Alabama whose hopes for children may depend on in vitro fertilization.

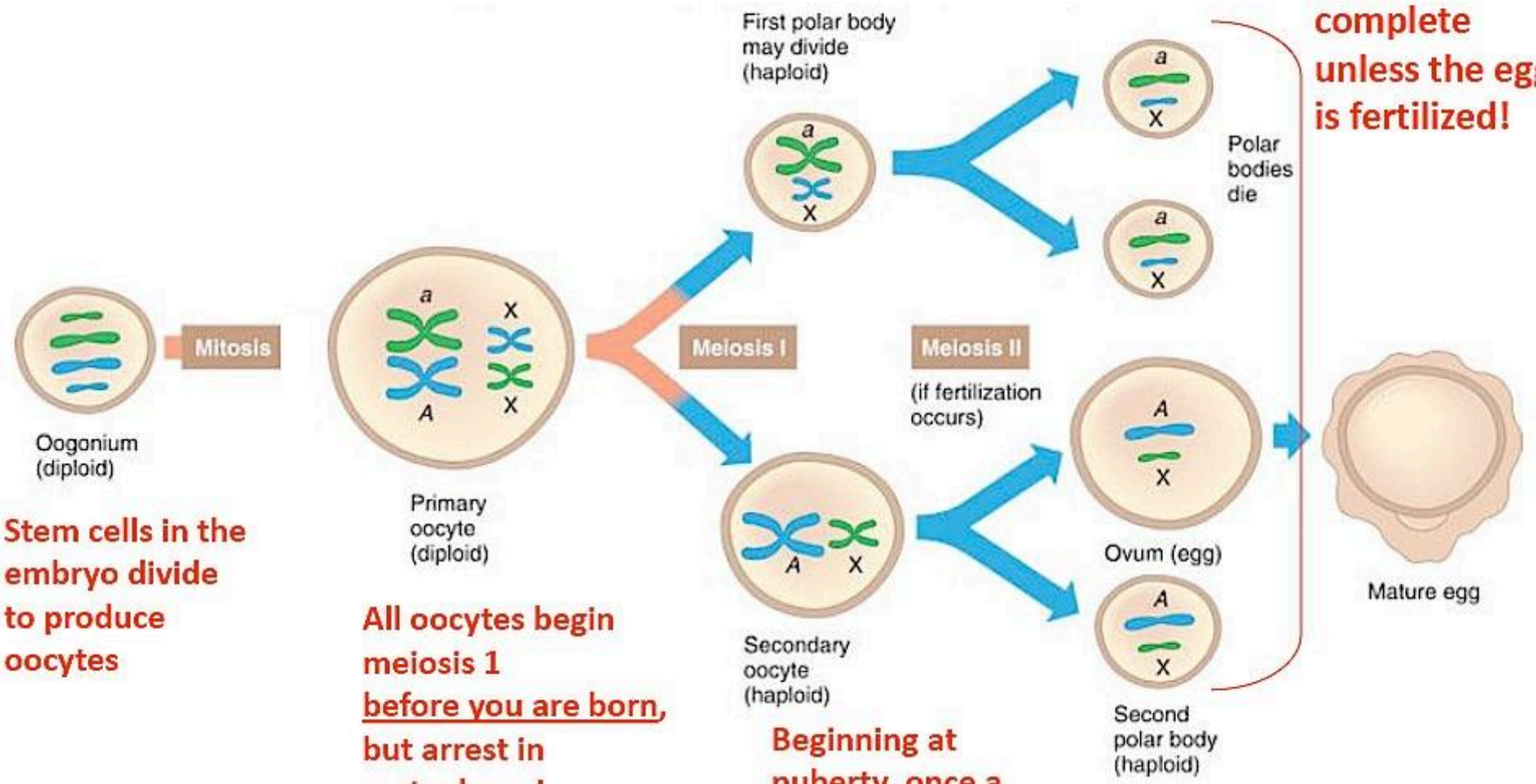

By Roni Caryn Rabin and Azeen Ghorayshi

Feb. 20, 2024

An Alabama Supreme Court's ruling that frozen embryos in test tubes should be considered children has sent shock waves through the world of reproductive medicine, casting doubt over fertility care for would-be parents in the state and raising complex legal questions with implications extending far beyond Alabama.


Cumulus
Polar body
Ovum
Cell membrane
Zona pellucida


Maturing oocytes
Fallopian tube
Primary oocyte
Developing follicle
Fertilization and meiosis II
Meiosis I
Secondary oocyte
Ovary
Ovulation
Ovum (egg)



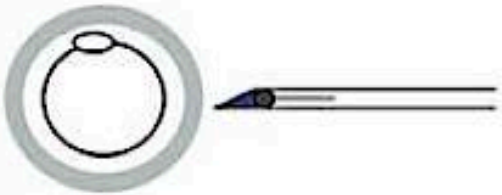
Stem cells in the embryo divide to produce oocytes

All oocytes begin meiosis 1 <u>before you are born</u>, but arrest in metaphase I

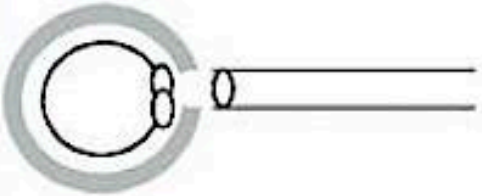
Beginning at puberty, once a month, a single ooctye is released from the oocyte ("ovulation") and finishes meiosis I

Meiosis II will not complete unless the egg is fertilized!

Day 1
Performance of ICSI (sperm injection)



6–10 h after ICSI: Extraction of 1st and 2nd polar body after opening the zona pellucida



Directly after biopsy: assessment of polar bodies, preparation, performance and analysis of FISH

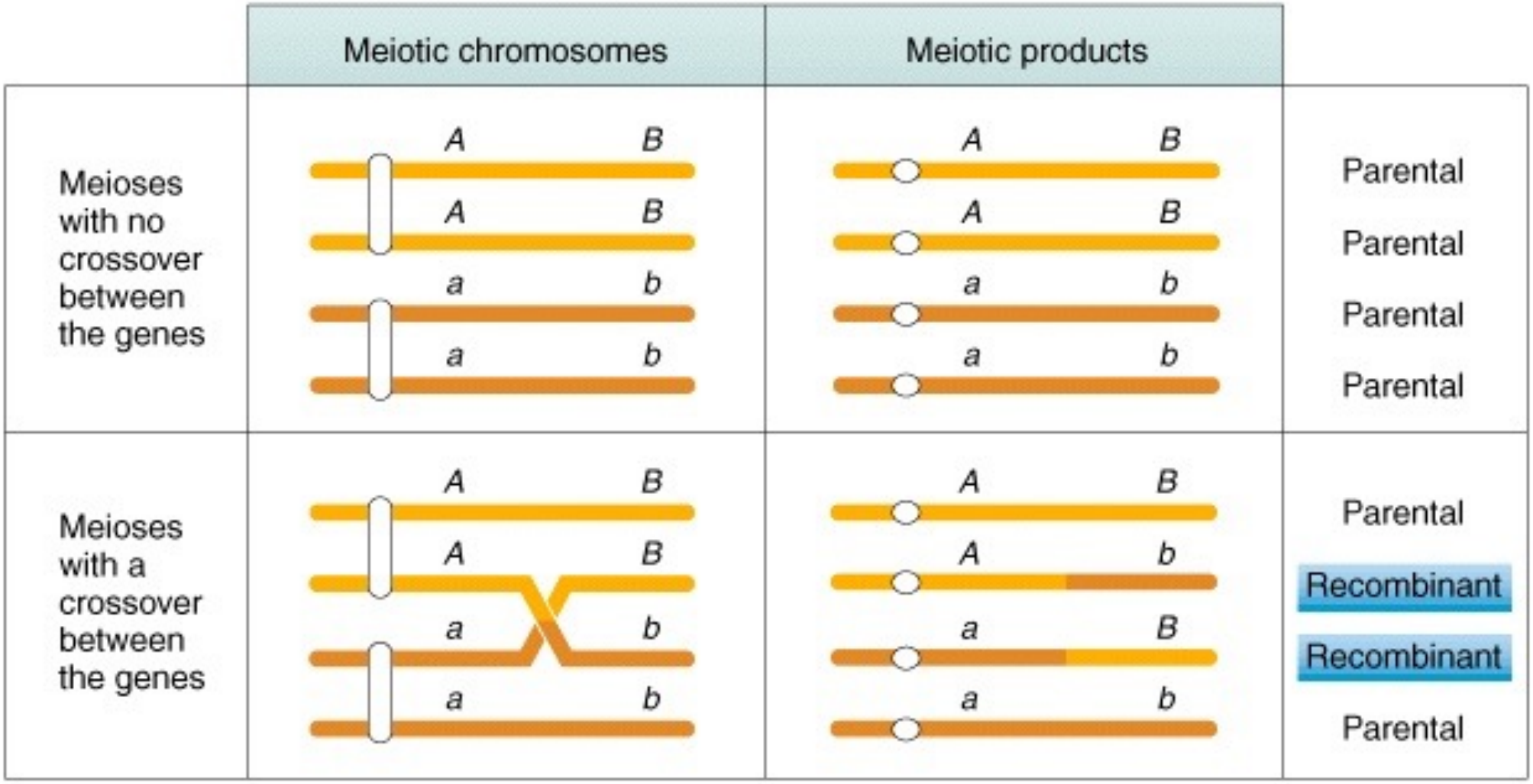
Day 2
20 h after ICSI: analysis of NPB distribution pattern in the pronuclei of the fertilized oocytes, informing of patients and decision

Further culture and transfer

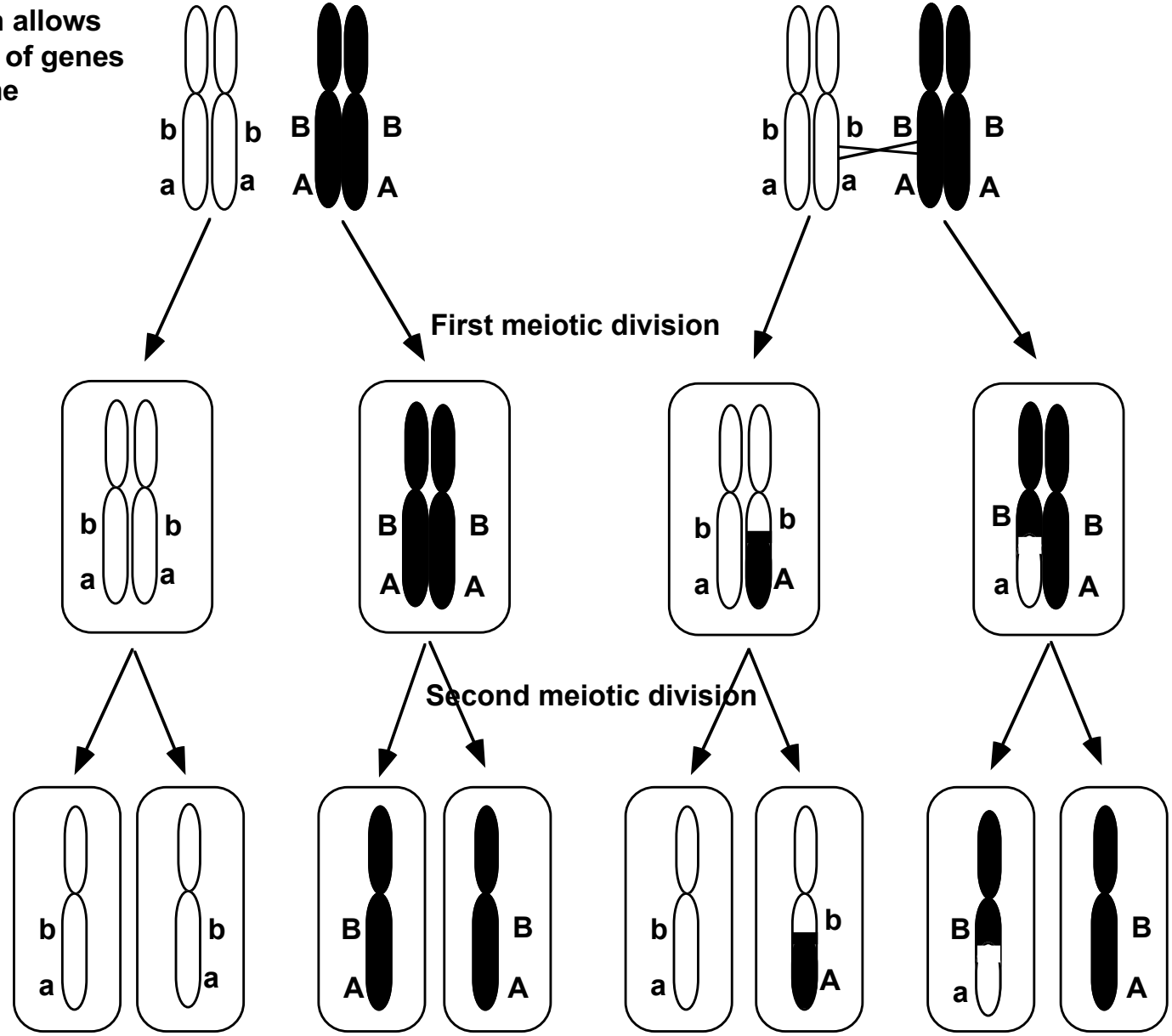
Cryopreservation

No further culture

MEIOTIC RECOMBINATION



meiotic recombination allows for shuffling of alleles of genes that reside on the same chromosome



Segregation of A-a at the first meiotic division

1. Segregation of A-a at the second meiotic division

2. New gamete combinations of the A and B genes

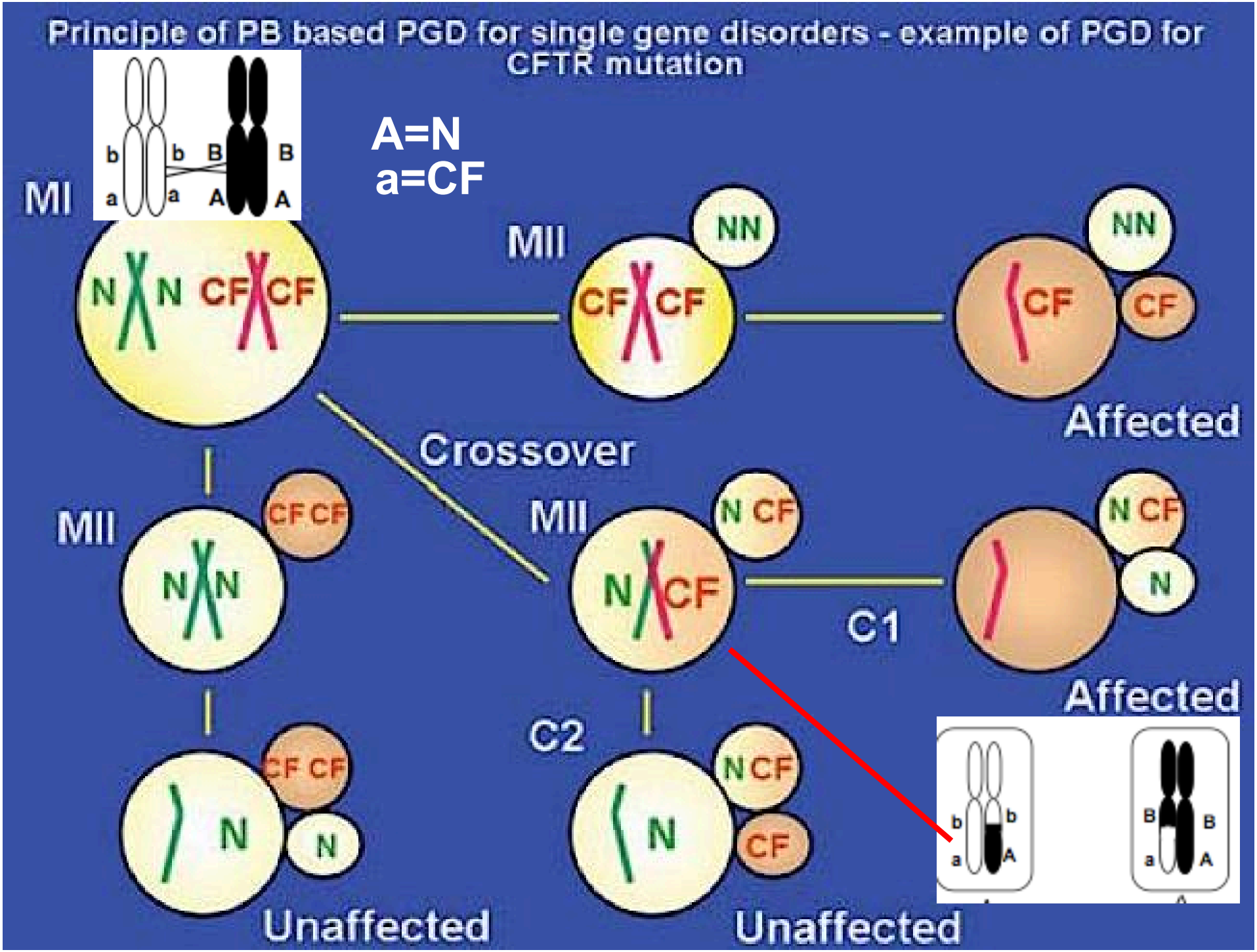
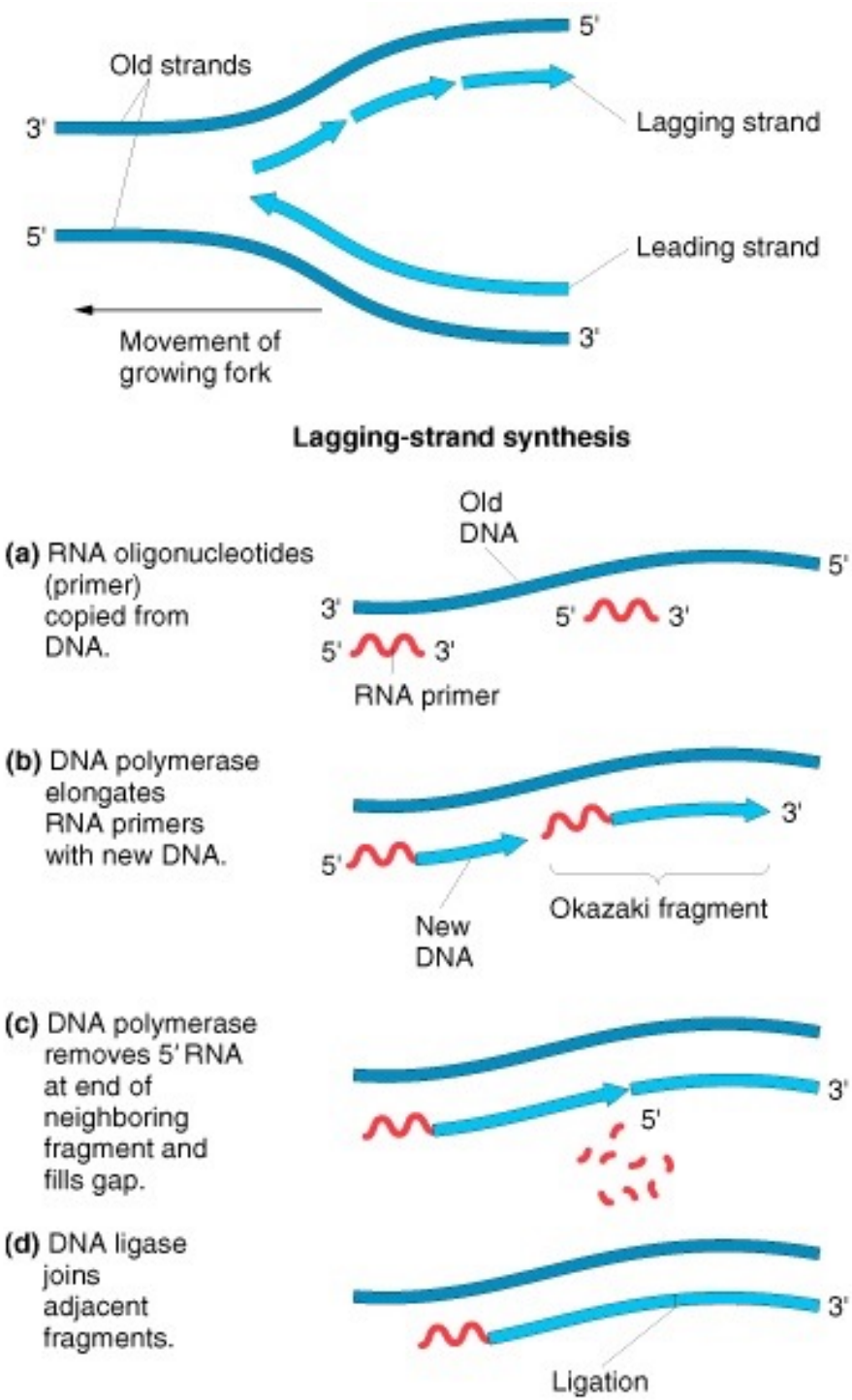

Principle of PB based PGD for single gene disorders - example of PGD for CFTR mutation
A=N
a=CF
MI
MII
MII
MII
Crossover
C1
C2
Affected
Affected
Unaffected
Unaffected
N N CF CF
CF CF
NN
CF
CF
N N
CF CF
N
N
N CF
N CF
N
N CF
CF
b b B B
a a A A

Figure 1 Principle of PB-based PGD for single-gene disorders—example of PGD for CFTR mutation. The large circle represents the genotype of oocyte obtained from heterozygous carrier of mutant gene prior to PB1 extrusion (metaphase I, MI). Other seven big circles show oocytes resulting from the first (metaphase II, MII) and second meiotic divisions. Seven smaller circles show extruded PB1s, and five smallest ones—PB2s. N, represents normal; CF, affected (CFTR) allele; C1 and C2, possible outcomes from heterozygous MII oocyte after the second meiotic division. Shaded circles represent oocytes and PBs containing mutant gene. Upper portion shows extrusion of homozygous normal PB1, resulting in affected oocyte, confirmed by mutant PB2 (shaded small circle), while left-hand portion presents opposite sequence of events. Crossover situation evidenced by heterozygous PB1 is shown in middle, resulting in either affected (C1) (evidenced by normal PB2 extrusion) or normal (C2) oocyte (evidenced by abnormal PB2 extrusion).

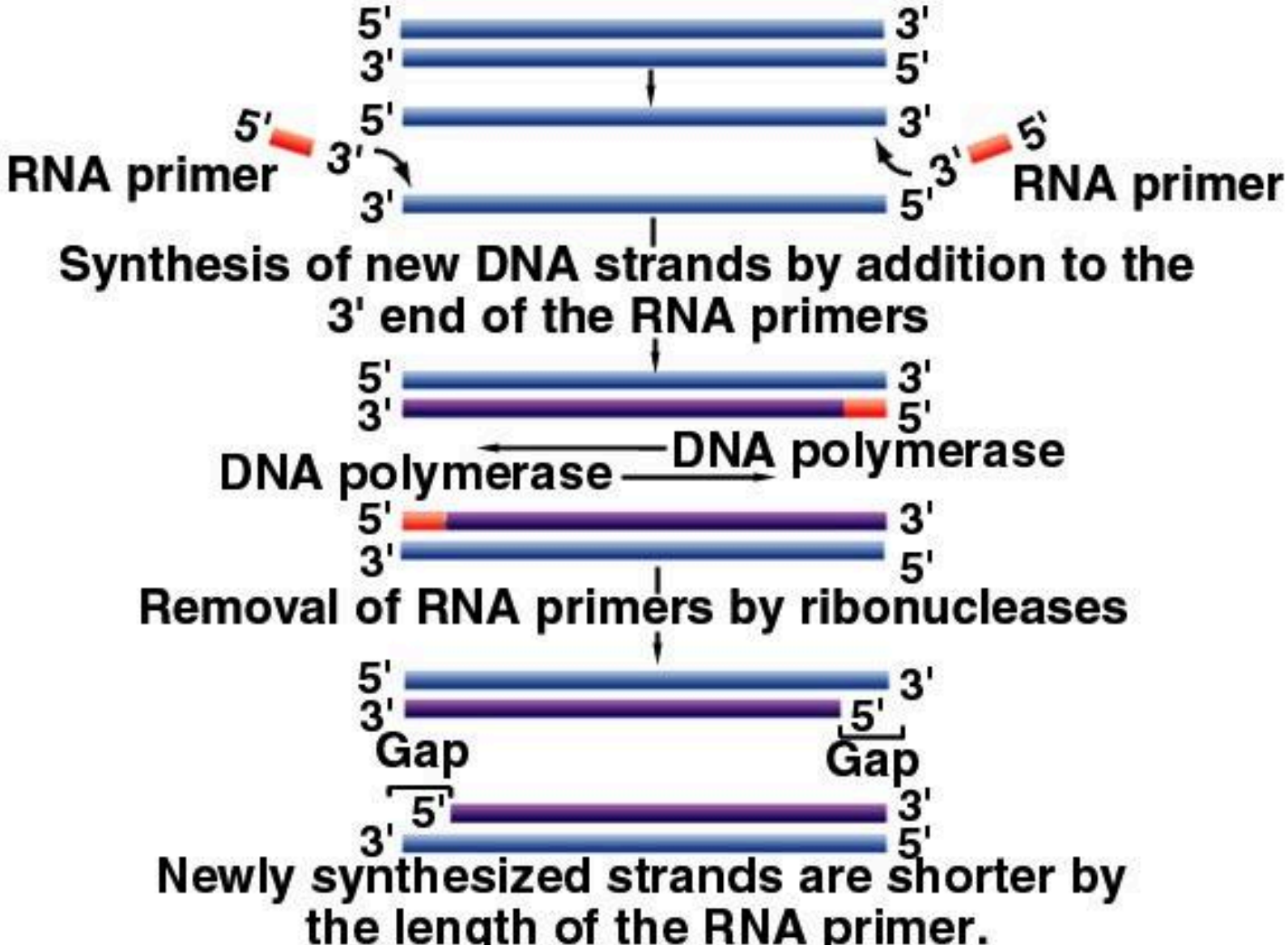
The inconstant genome: Telomeres

DNA synthesis occurs 5'-3'

DNA synthesis is initiated using RNA primers, which are ultimately degraded.



Problems at the 5' -end of DNA



The implication ……..

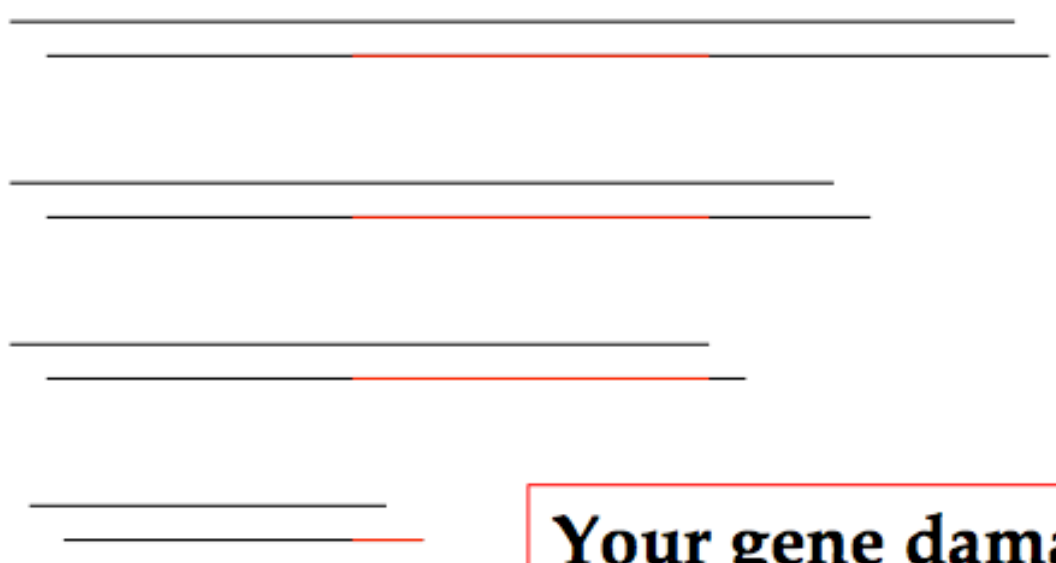
-

Division 0

Division 1

Division 2

Division n



Your gene damaged!

Your important gene

The Nobel Prize in Physiology or Medicine 2009

Elizabeth H. Blackburn, Carol W. Greider, Jack W. Szostak

Photo: U. Montan

Elizabeth H. Blackburn

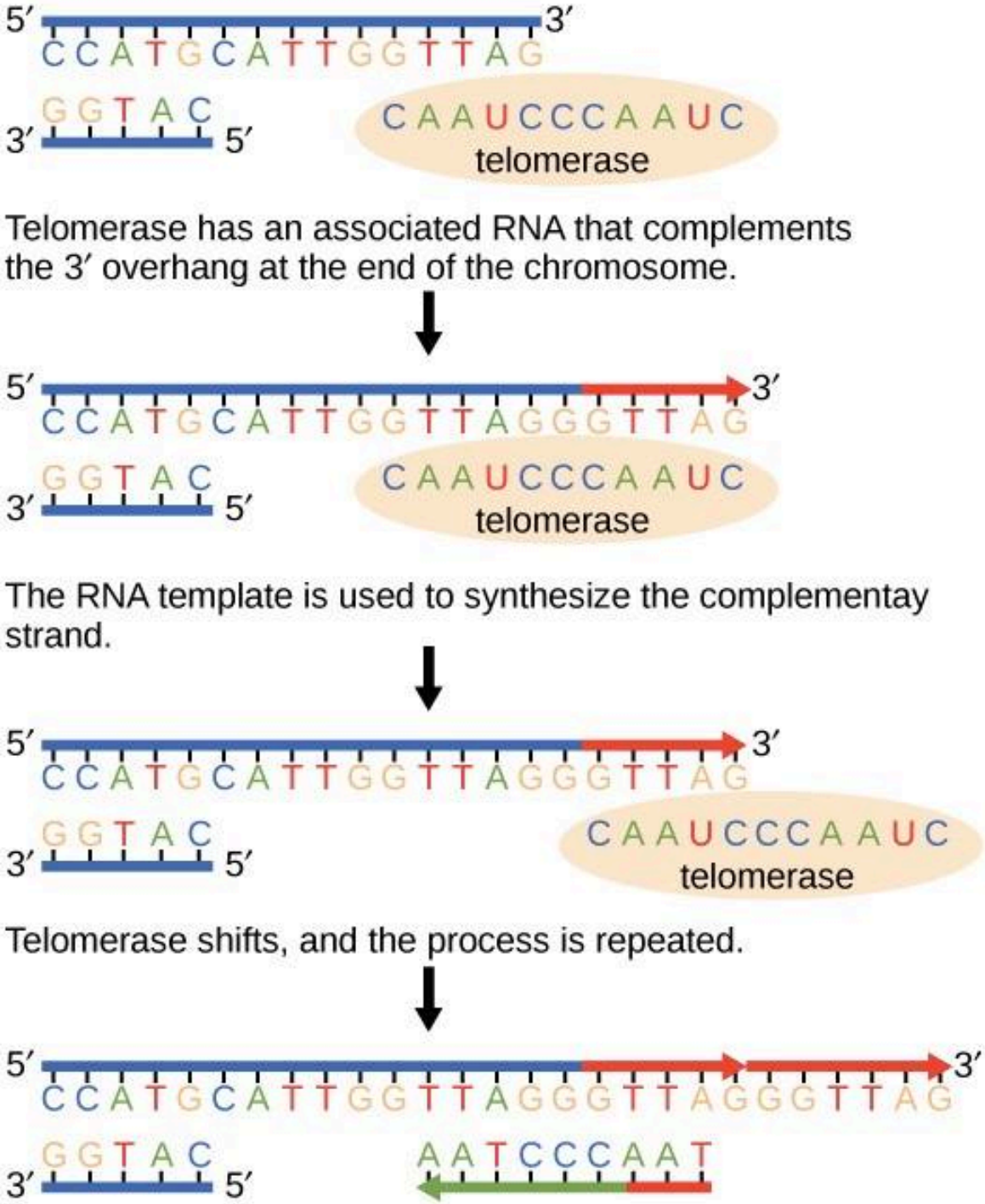
Photo: U. Montan

Carol W. Greider

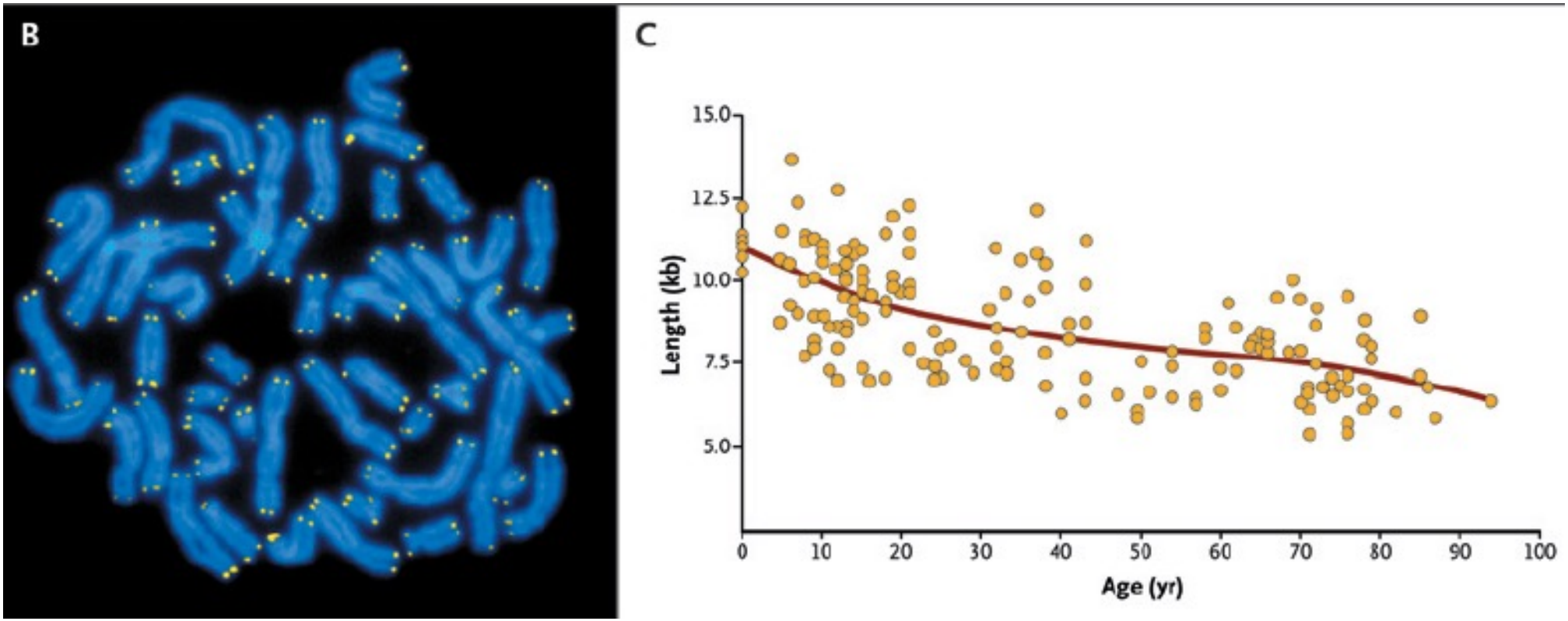
Photo: U. Montan

Jack W. Szostak

The Nobel Prize in Physiology or Medicine 2009 was awarded jointly to Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak *"for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"*.


5′
3′
C C A T G C A T T G G T T A G
G G T A C
3′
5′
C A A U C C C A A U C
telomerase
Telomerase has an associated RNA that complements the 3′ overhang at the end of the chromosome.
5′
3′
C C A T G C A T T G G T T A G G G T T A G
G G T A C
3′
5′
C A A U C C C A A U C
telomerase
The RNA template is used to synthesize the complementay strand.
5′
3′
C C A T G C A T T G G T T A G G G T T A G
G G T A C
3′
5′
C A A U C C C A A U C
telomerase
Telomerase shifts, and the process is repeated.
5′
3′
C C A T G C A T T G G T T A G G G T T A G G G T T A G
G G T A C
3′
5′
A A T C C C A A T
Primase and DNA polymerase syntesize the complementary strand.

Telomeres at the ends of chromosomes that have undergone DNA replication (two dots per chromosome end)



Telomeres shrink with age

The 3’ overhang at the end of a chromosome telomere is protected by a cap composed of multiple proteins. This keeps it from being degraded and/or recognized as a DNA break

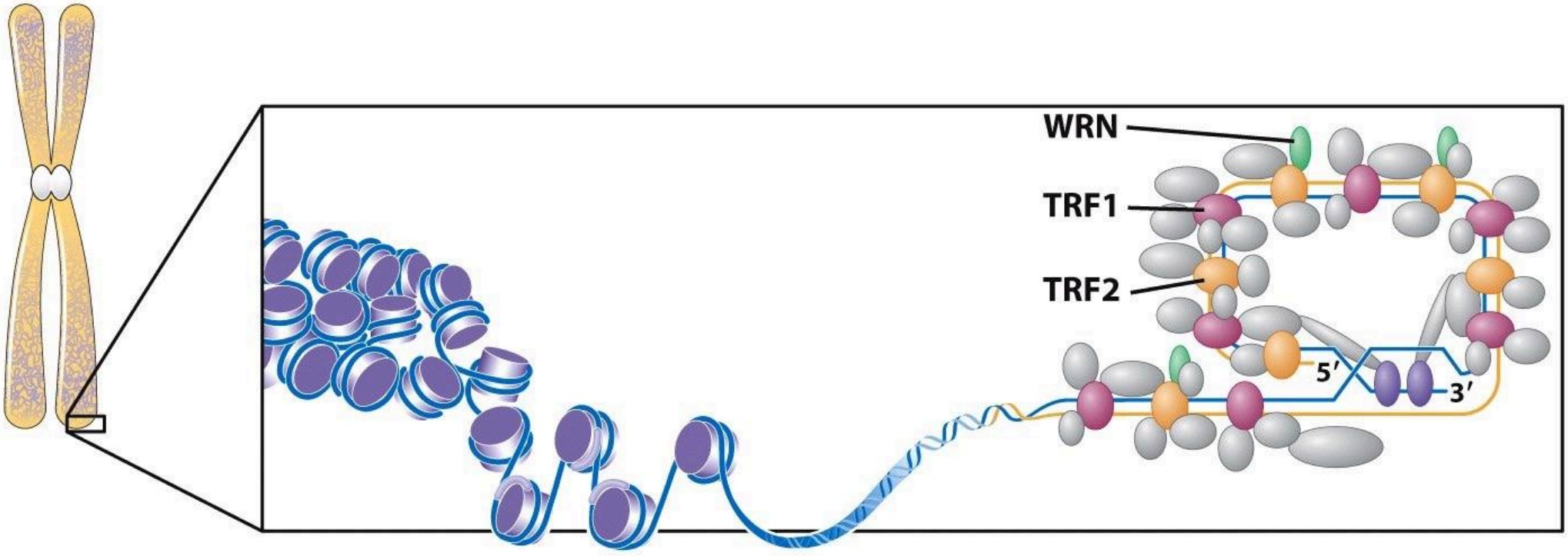


Figure 7-29
Introduction to Genetic Analysis, Tenth Edition

The implication ……..

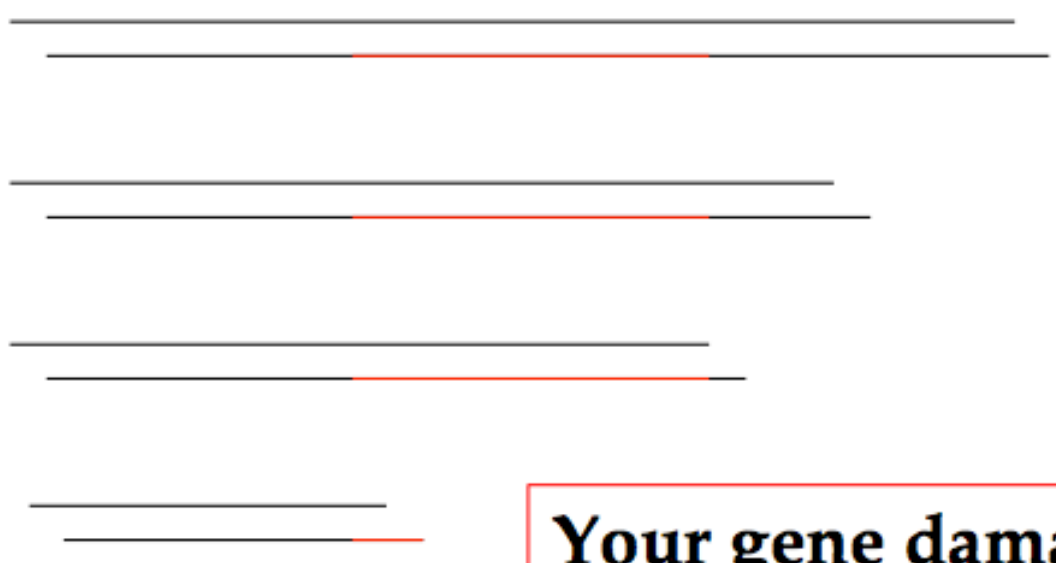
-

Division 0

Division 1

Division 2

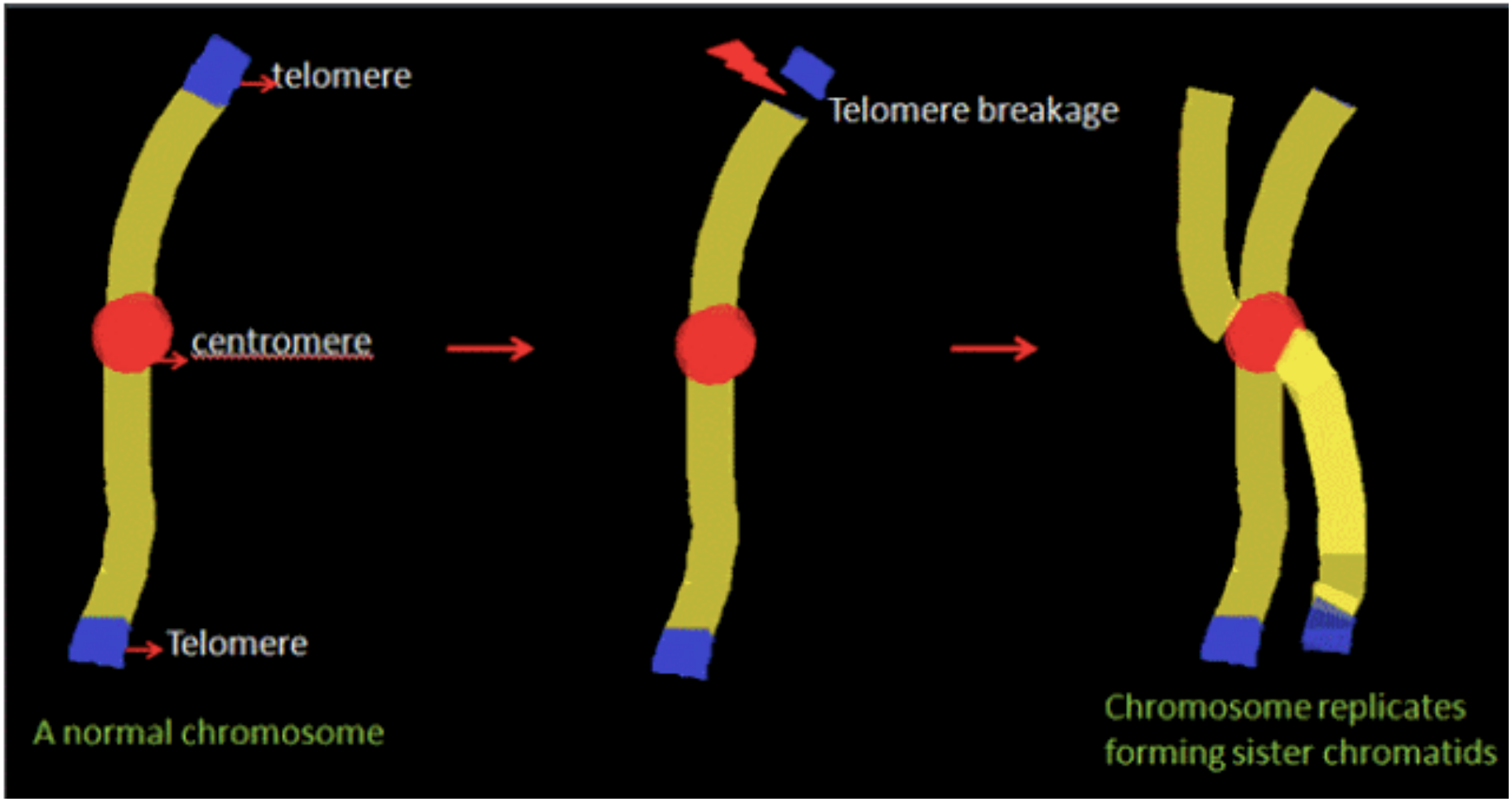
Division n



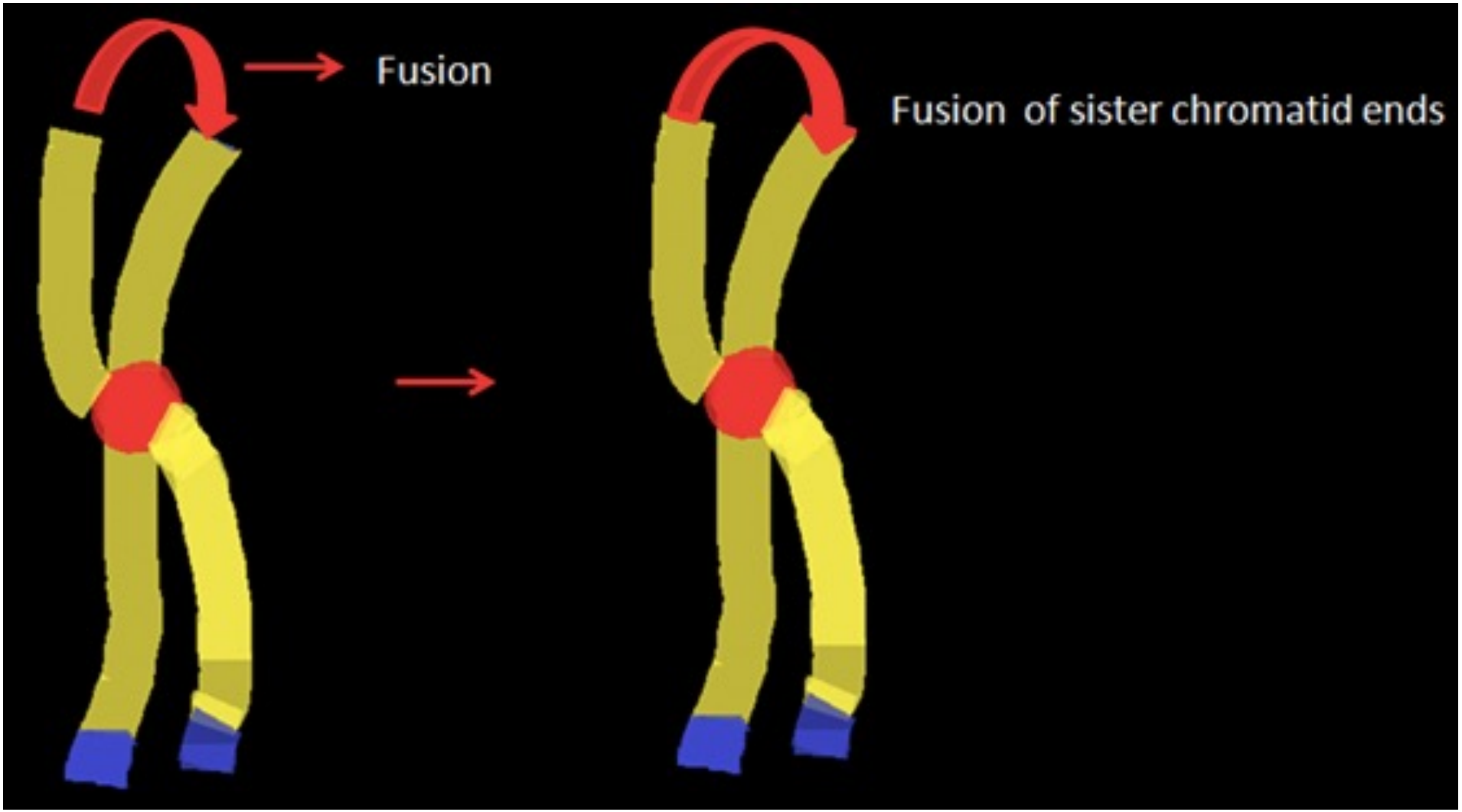
Your gene damaged!

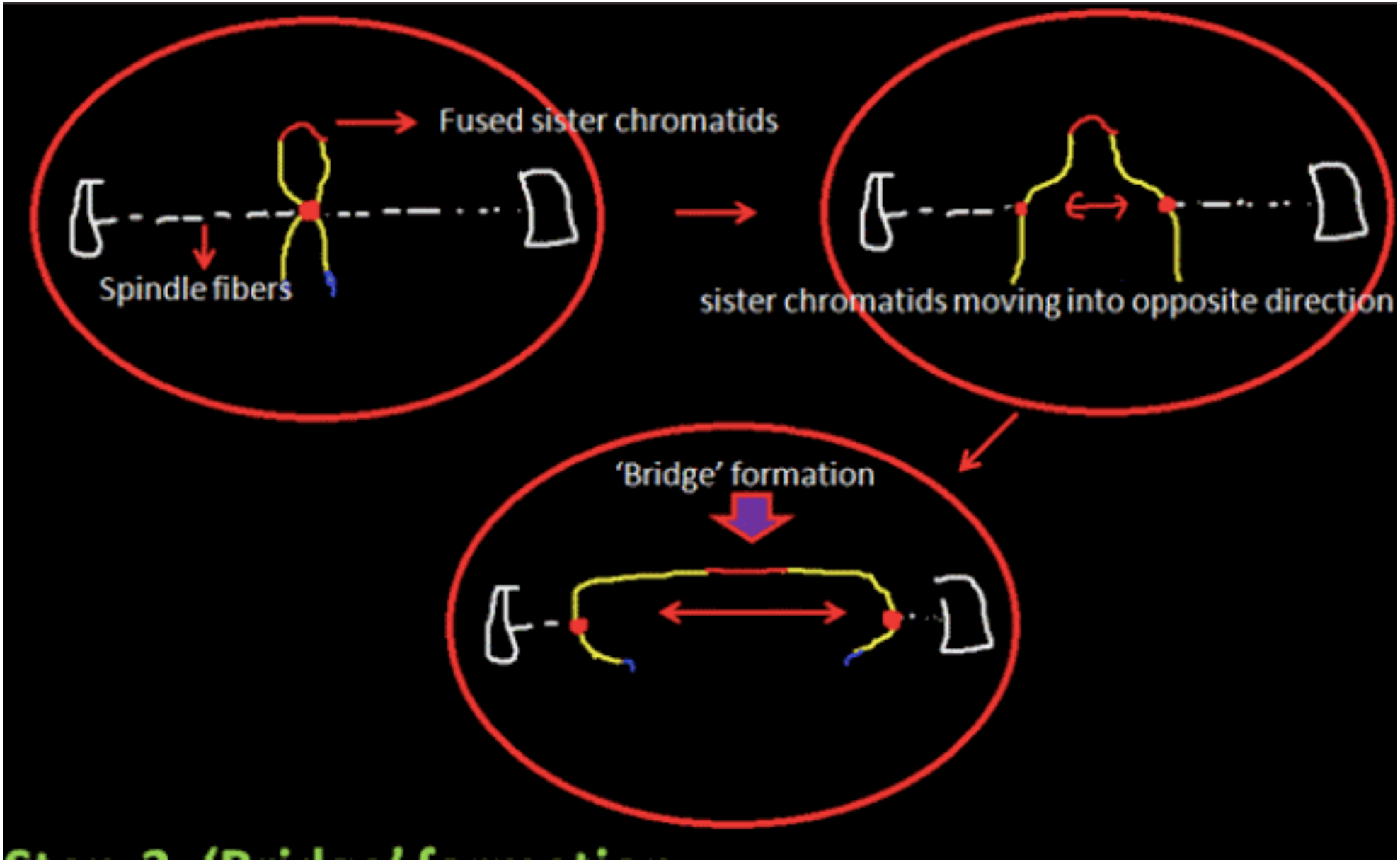
Your important gene

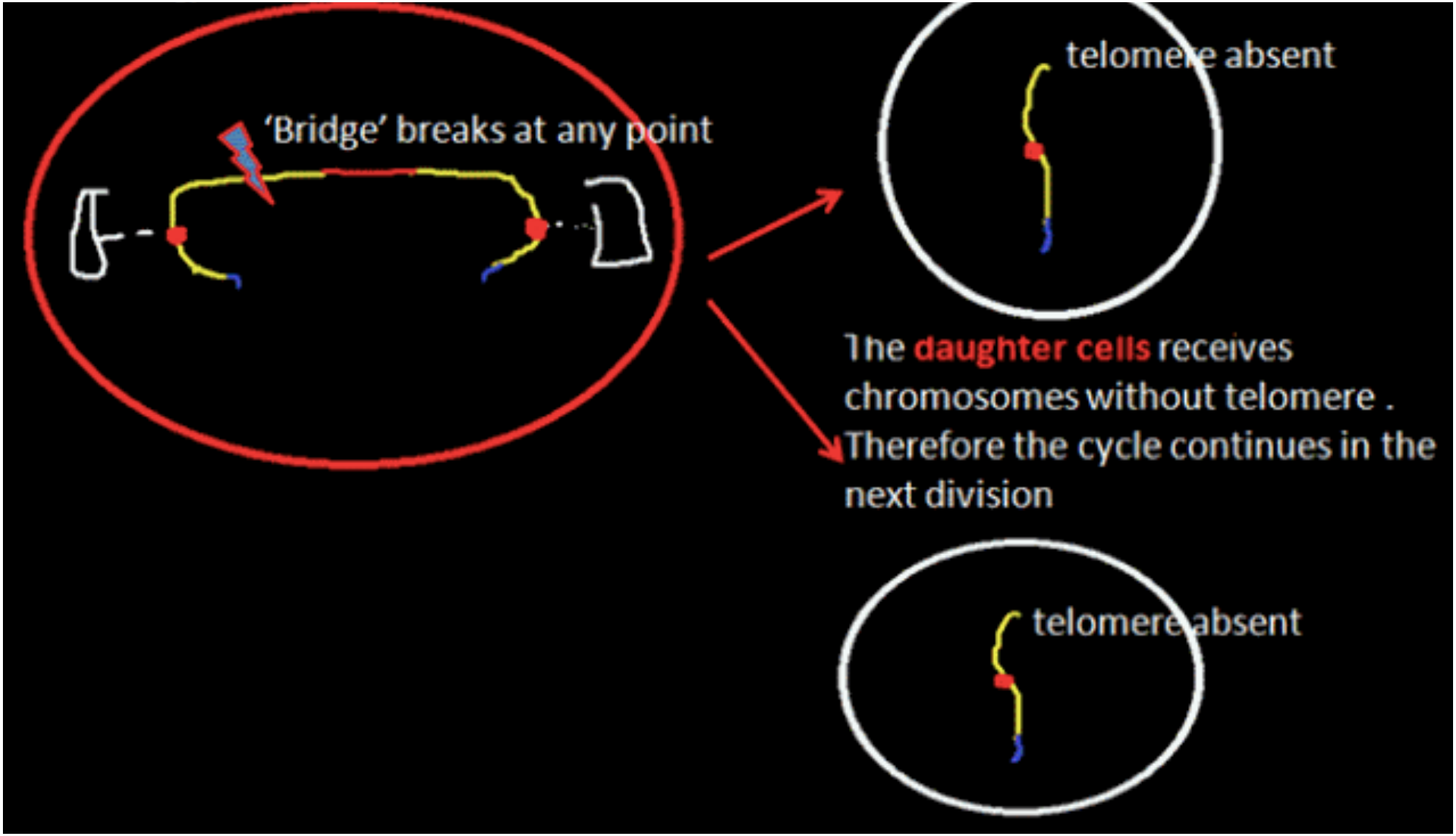
Step 1: Breakage



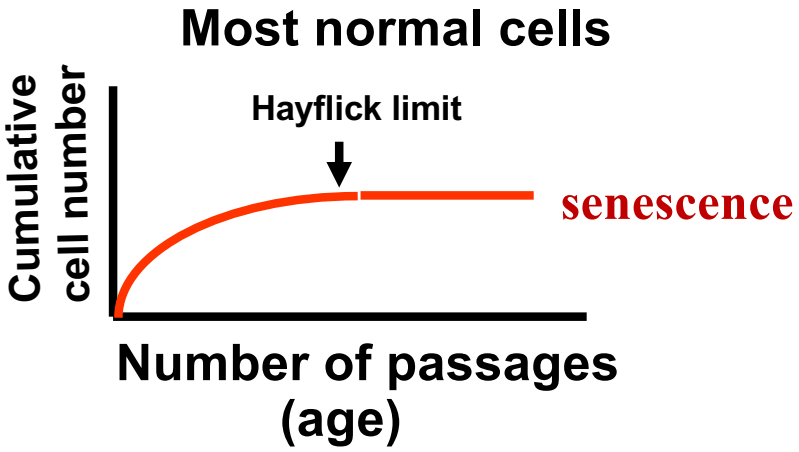
Chromosomes that lack telomeres appear to the cell as DNA damage. The cell attempts repair by ligating any nearby ends together as a "quick fix"



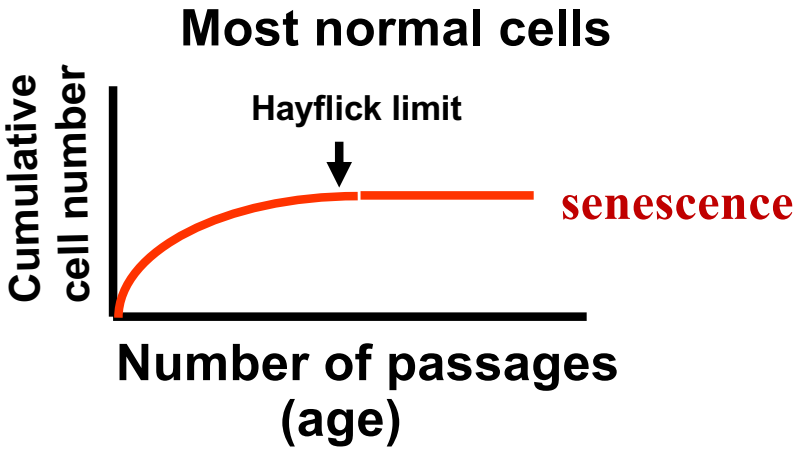

Fused sister chromatids
Spindle fibers
sister chromatids moving into opposite direction
'Bridge' formation

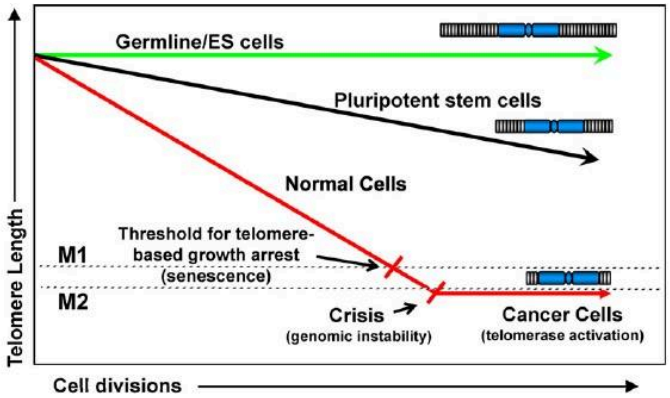

'Bridge' breaks at any point
telomere absent
The daughter cells receives chromosomes without telomere .
Therefore the cycle continues in the next division
telomere absent

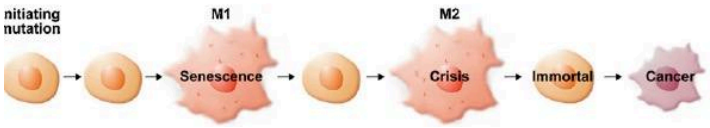
Most normal somatic cells can only replicate a finite number of times



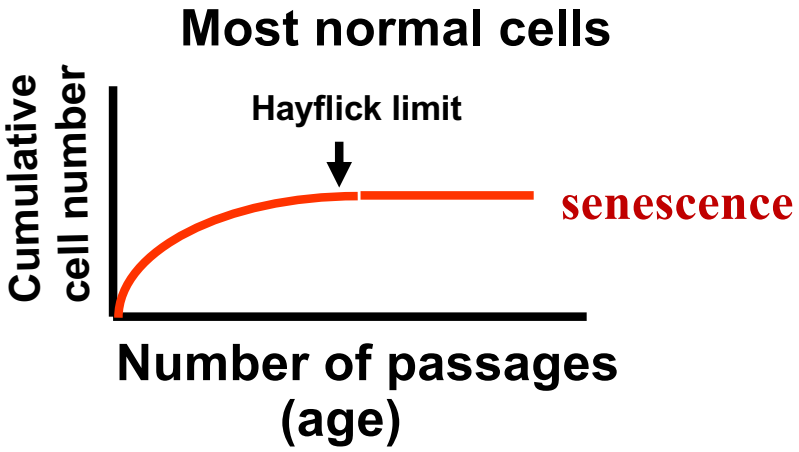
Most normal somatic cells can only replicate a finite number of times

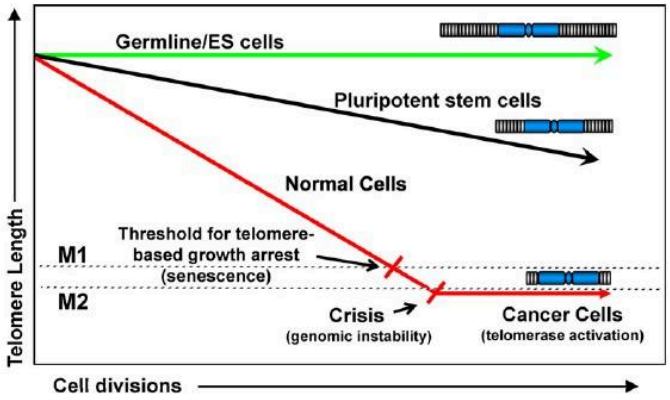


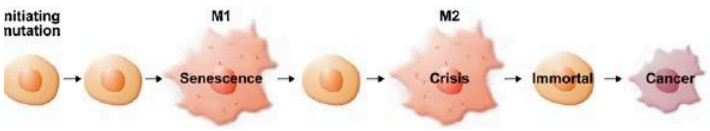


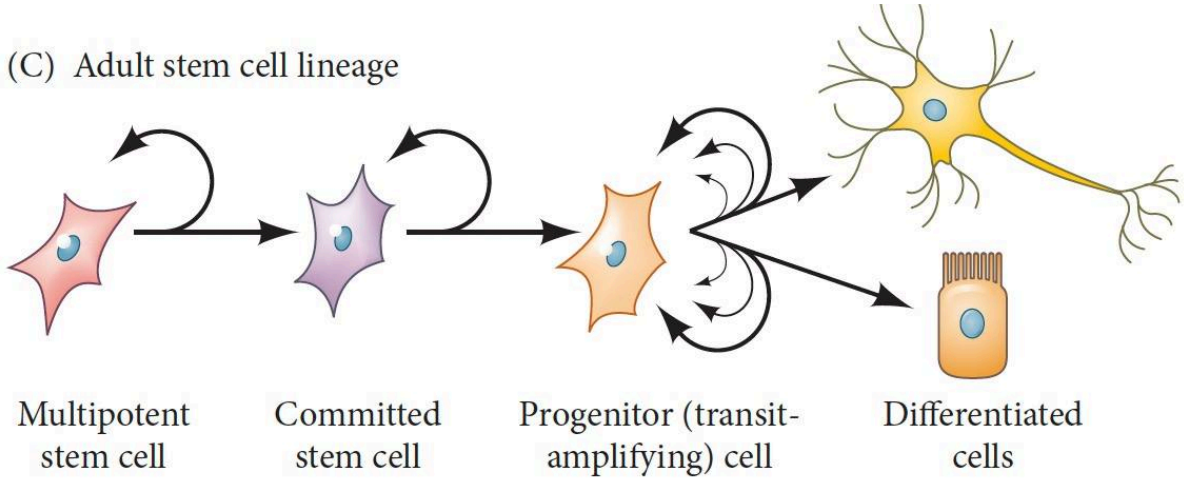


Most normal somatic cells can only replicate a finite number of times

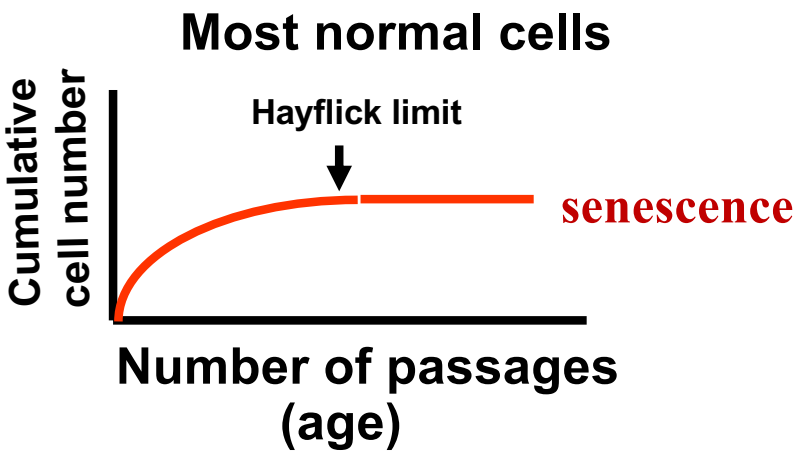


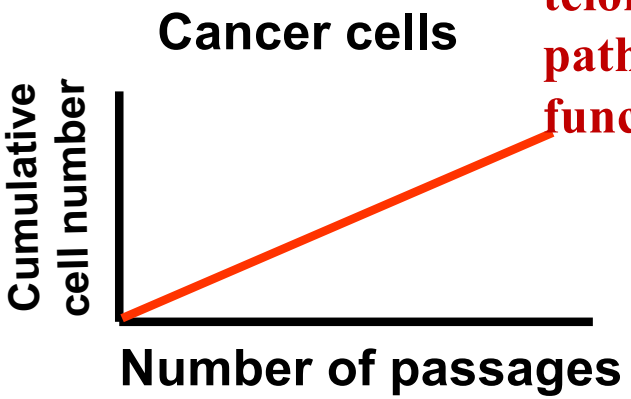




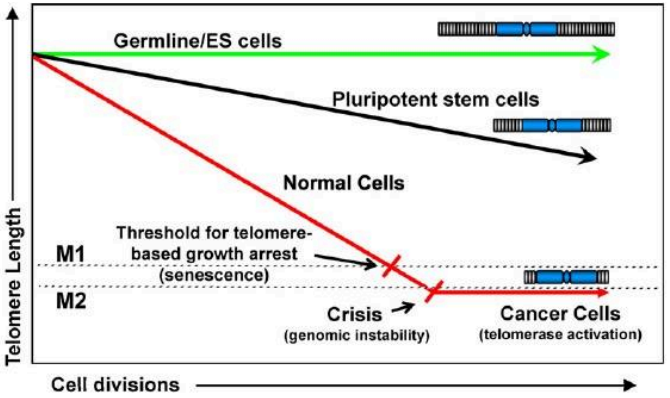


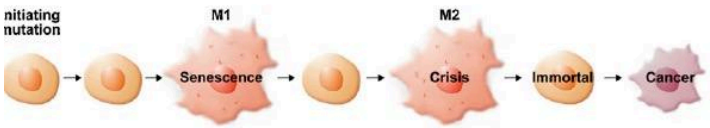
Most normal somatic cells can only replicate a finite number of times

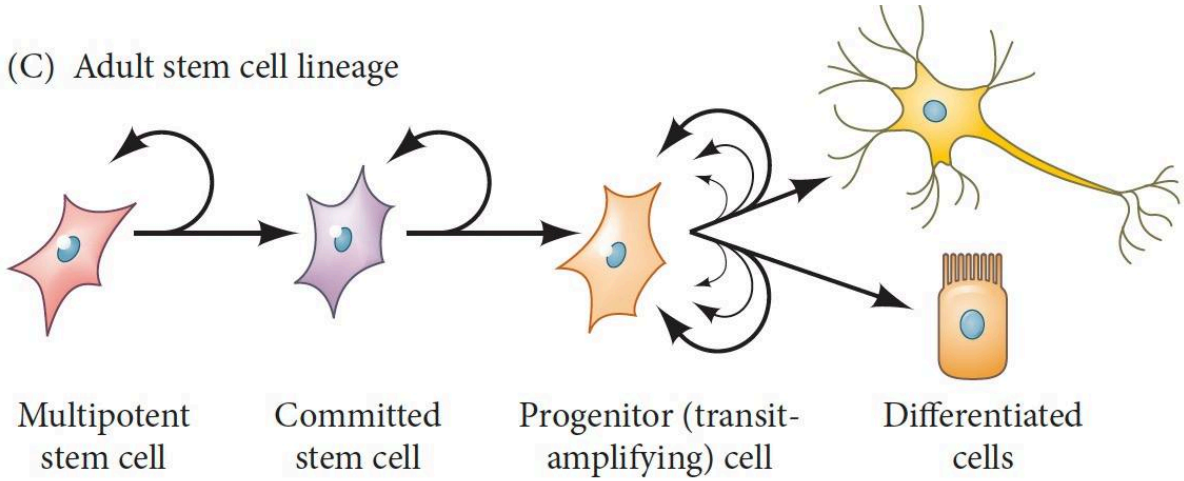




ALL cancers reactivate telomerase or an alternative pathway that serves the same function







Telomere shortening rate predicts species life span

Kurt Whittemore[a], Elsa Vera[a], Eva Martínez-Nevado[b], Carola Sanpera[c,d], and Maria A. Blasco[a,1]

[a]Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Research Centre, 28029 Madrid, Spain; [b]Veterinary Department, Madrid-Zoo Aquarium, 28011 Madrid, Spain; [c]Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Facultat de Biologia, Universitat de Barcelona, 08028 Barcelona, Spain; and [d]Institut de Recerca de la Biodiversitat, Universitat de Barcelona, 08028 Barcelona, Spain

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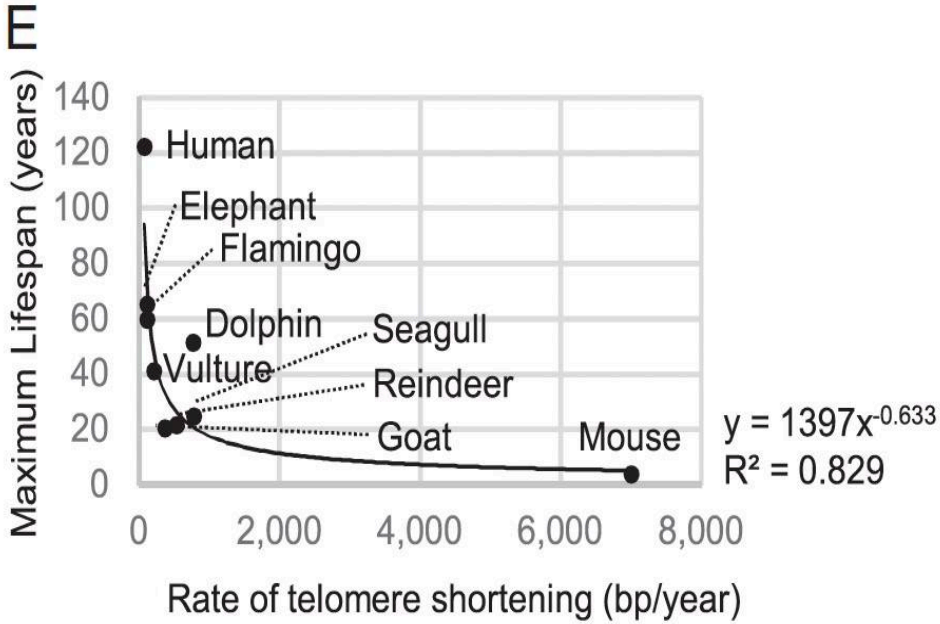
Telomere shortening to a critical length can trigger aging and shorter life spans in mice and humans by a mechanism that involves induction of a persistent DNA damage response at chromosome ends and loss of cellular viability. However, whether telomere length is a universal determinant of species longevity is not known. To determine whether telomere shortening can be a single parameter to predict species longevities, here we measured in parallel the telomere length of a wide variety of species (birds and mammals) with very different life spans and body sizes, including mouse (*Mus musculus*), goat (*Capra hircus*), Audouin's gull (*Larus audouinii*), reindeer (*Rangifer tarandus*), griffon vulture (*Gyps fulvus*), bottlenose dolphin (*Tursiops truncatus*), American flamingo (*Phoenicopterus ruber*), and Sumatran elephant (*Elephas maximus sumatranus*). We found that the telomere shortening rate, but not the initial telomere length alone, is a powerful predictor of species life span. These results support the notion that critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of species life span.

previously shown a rate of telomere shortening of around 7,000 bp per y, which is 100-fold faster than that reported in humans (4).



LETTER

doi:10.1038/nature09603

Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice

Mariela Jaskelioff[1], Florian L. Muller[1], Ji-Hye Paik[1], Emily Thomas[1], Shan Jiang[1], Andrew C. Adams[2], Ergun Sahin[1], Maria Kost-Alimova[1], Alexei Protopopov[1], Juan Cadiñanos[1], James W. Horner[1], Eleftheria Maratos-Flier[2] & Ronald A. DePinho[1]

An ageing world population has fuelled interest in regenerative remedies that may stem declining organ function and maintain fitness. Unanswered is whether elimination of intrinsic instigators driving age-associated degeneration can reverse, as opposed to simply arrest, various afflictions of the aged. Such instigators include progressively damaged genomes. Telomerase-deficient mice have served as a model system to study the adverse cellular and organismal consequences of wide-spread endogenous DNA damage signalling activation *in vivo*[1]. Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure and impaired tissue injury responses[1]. Here, we sought to determine whether entrenched multi-system degeneration in adult mice with severe telomere dysfunction can be halted or possibly reversed by reactivation of endogenous telomerase activity. To this end, we engineered a knock-in allele encoding a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-oestrogen receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter. Homozygous TERT-ER mice have short dysfunctional telomeres and sustain increased DNA damage signalling and classical degenerative phenotypes upon successive generational matings and advancing age. Telomerase reactivation in such late generation TERT-ER mice extends telomeres, reduces DNA damage signalling and associated cellular checkpoint responses, allows resumption of proliferation in quiescent cultures, and eliminates degenerative phenotypes across multiple organs including testes, spleens and intestines. Notably,

onset of tissue atrophy and organ system failure in degenerative diseases such as ataxia-telangiectasia, Werner syndrome, dyskeratosis congenita and liver cirrhosis, among others[1,3]. In cell-based models of ataxia-telangiectasia and Werner syndrome, enforced TERT can restore normal cellular proliferative potential[8]. These findings build on seminal cell culture studies showing that enforced TERT expression can endow primary human cells with unlimited replicative potential[9]. Importantly, TERT overexpression in epithelial tissues of cancer-resistant mice leads to extended median lifespan[10]. In addition, intercrossing wild-type and late generation $mTerc^{-/-}$ mice with severe degenerative phenotypes results in healthy offspring[11], indicating that viable late generation $mTerc^{-/-}$ germ cells can be restored to normal telomere function on introduction of a wild-type *mTerc* allele at the time of fertilization. However, to our knowledge, there are no genetic or pharmacological studies showing somatic reversal of age-related degenerative phenotypes driven by endogenous genotoxic stresses in adult mammals. Here, in telomerase-deficient mice experiencing severe tissue degeneration, we investigated whether endogenous telomerase-mediated restoration of telomere function throughout the organism would quell DNA damage signalling and either arrest, or possibly reverse, cellular checkpoint responses and associated tissue atrophy and dysfunction. Notably, the mice enlisted into this study are adults exhibiting significant progeroid phenotypes.

Construction and functional validation of the germline TERT-ER knock-in allele are detailed in Supplementary Fig. 1. In the absence of 4-OHT, ER fusion proteins remain in an inactive misfolded state[12] and thus we first sought to verify whether mice homozygous for TERT-ER

Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians

Gil Atzmon[a,b,1,2], Miook Cho[a,1], Richard M. Cawthon[c], Temuri Budagov[b], Micol Katz[b], Xiaoman Yang[b], Glenn Siegel[b], Aviv Bergman[d], Derek M. Huffman[a,b], Clyde B. Schechter[e], Woodring E. Wright[f], Jerry W. Shay[f], Nir Barzilai[a,b], Diddahally R. Govindaraju[g], and Yousin Suh[a,b,2]

[a]Departments of Medicine and Genetics, Albert Einstein College of Medicine, Bronx, NY 10461; [b]Institute for Aging Research, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY 10461; [c]Department of Human Genetics, University of Utah, Salt Lake City, UT 84112; [d]Department of Systems and Computational Biology, Albert Einstein College of Medicine, Bronx, NY 10461; [e]Department of Family and Social Medicine, Albert Einstein College of Medicine, Bronx, NY 10461; [f]Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390; and [g]Department of Neurology, Boston University School of Medicine, Boston, MA 02118

Edited by Stephen Curtis Stearns, Yale University, New Haven, CT, and accepted by the Editorial Board October 7, 2009 (received for review July 20, 2009)

Telomere length in humans is emerging as a biomarker of aging because its shortening is associated with aging-related diseases and early mortality. However, genetic mechanisms responsible for these associations are not known. Here, in a cohort of Ashkenazi Jewish centenarians, their offspring, and offspring-matched controls, we studied the inheritance and maintenance of telomere length and variations in two major genes associated with telomerase enzyme activity, *hTERT* and *hTERC*. We demonstrated that centenarians and their offspring maintain longer telomeres compared with controls with advancing age and that longer telomeres are associated with protection from age-related diseases, better cognitive function, and lipid profiles of healthy aging. Sequence analysis of *hTERT* and *hTERC* showed overrepresentation of synonymous and intronic mutations among centenarians relative to controls. Moreover, we identified a common *hTERT* haplotype that is associated with both exceptional longevity and longer telomere length. Thus, variations in human telomerase gene that are associated with better maintenance of telomere length may confer healthy aging and exceptional longevity in humans.

quantitative traits (16). Heritability estimates for telomere length vary from 35 to 80% (9, 13, 17). Although several candidate genes have been identified as potential modulators of telomere length in humans (17, 18), none of these genes seem to play a direct role in maintenance of telomere length (19). Recently, one of the most obvious candidate genes of telomere maintenance, telomerase, has been shown to play a direct role in the maintenance of telomere length in humans (20). Telomerase is a specialized ribonucleoprotein enzyme complex that adds telomere repeats to the ends of chromosomes and has two essential components: a catalytic component encoded by the human telomerase reverse transcriptase (hTERT) and a human telomerase RNA component (hTERC). The latter component provides the template for nucleotide addition by hTERT. Heterozygote mutations in the *hTERT* and *hTERC* genes lead to short telomeres and are the major risk factors for rare hematopoietic disorders of bone marrow failure, including aplastic anemia and dyskeratosis congenital. These results indicate that the levels of functional telomerase are critical for telomere maintenance (21).

telomerase is necessary but not sufficient for cancer

Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer

Bruno Bernardes de Jesus[1], *Elsa Vera*[1], *Kerstin Schneeberger*[1], *Agueda M. Tejera*[1], *Eduard Ayuso*[2,3], *Fatima Bosch*[2,3], *Maria A. Blasco*[1*]

Keywords: AAV9; aging; gene therapy; health span; TERT

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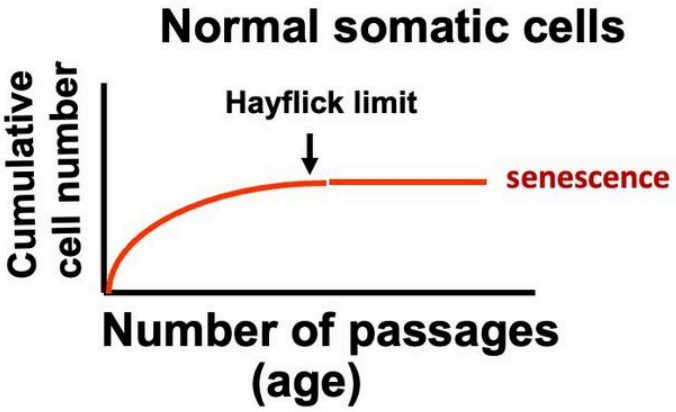
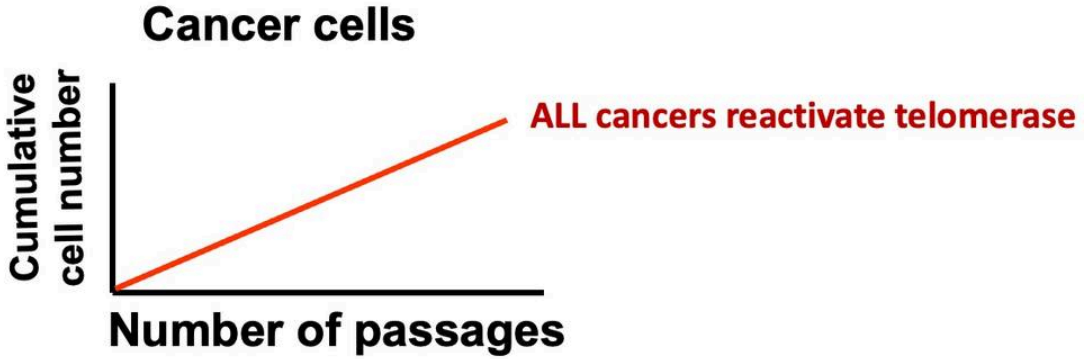
Revised March 29, 2012
Accepted March 30, 2012

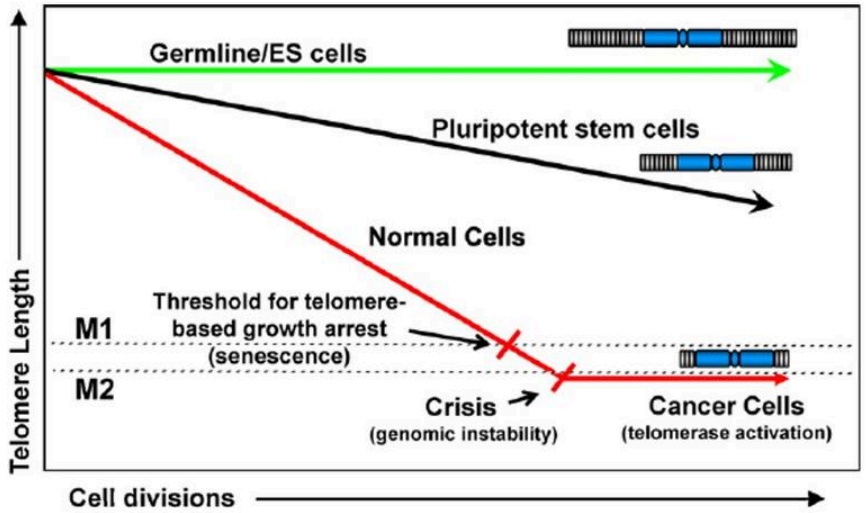
→See accompanying article
http://dx.doi.org/10.1002/emmm.201200246

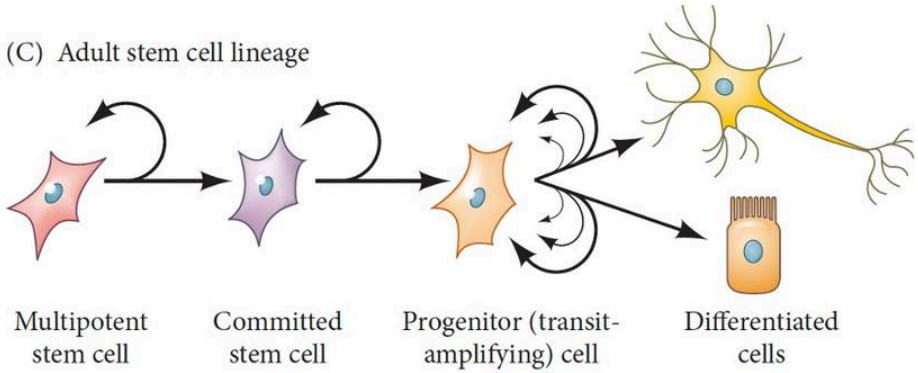
A major goal in aging research is to improve health during aging. In the case of mice, genetic manipulations that shorten or lengthen telomeres result, respectively, in decreased or increased longevity. Based on this, we have tested the effects of a telomerase gene therapy in adult (1 year of age) and old (2 years of age) mice. Treatment of 1- and 2-year old mice with an adeno associated virus (AAV) of wide tropism expressing mouse TERT had remarkable beneficial effects on health and fitness, including insulin sensitivity, osteoporosis, neuromuscular coordination and several molecular biomarkers of aging. Importantly, telomerase-treated mice did not develop more cancer than their control littermates, suggesting that the known tumorigenic activity of telomerase is severely decreased when expressed in adult or old organisms using AAV vectors. Finally, telomerase-treated mice, both at 1-year and at 2-year of age, had an increase in median lifespan of 24 and 13%, respectively. These beneficial effects were not observed with a catalytically inactive TERT, demonstrating that they require telomerase activity. Together, these results constitute a proof-of-principle of a role of TERT in delaying physiological aging and extending longevity in normal mice through a telomerase-based treatment, and demonstrate the feasibility of anti-aging gene therapy.

Being able to divide only a finite number of times provides a hard stop on lifespan, but also works to prevent cancer





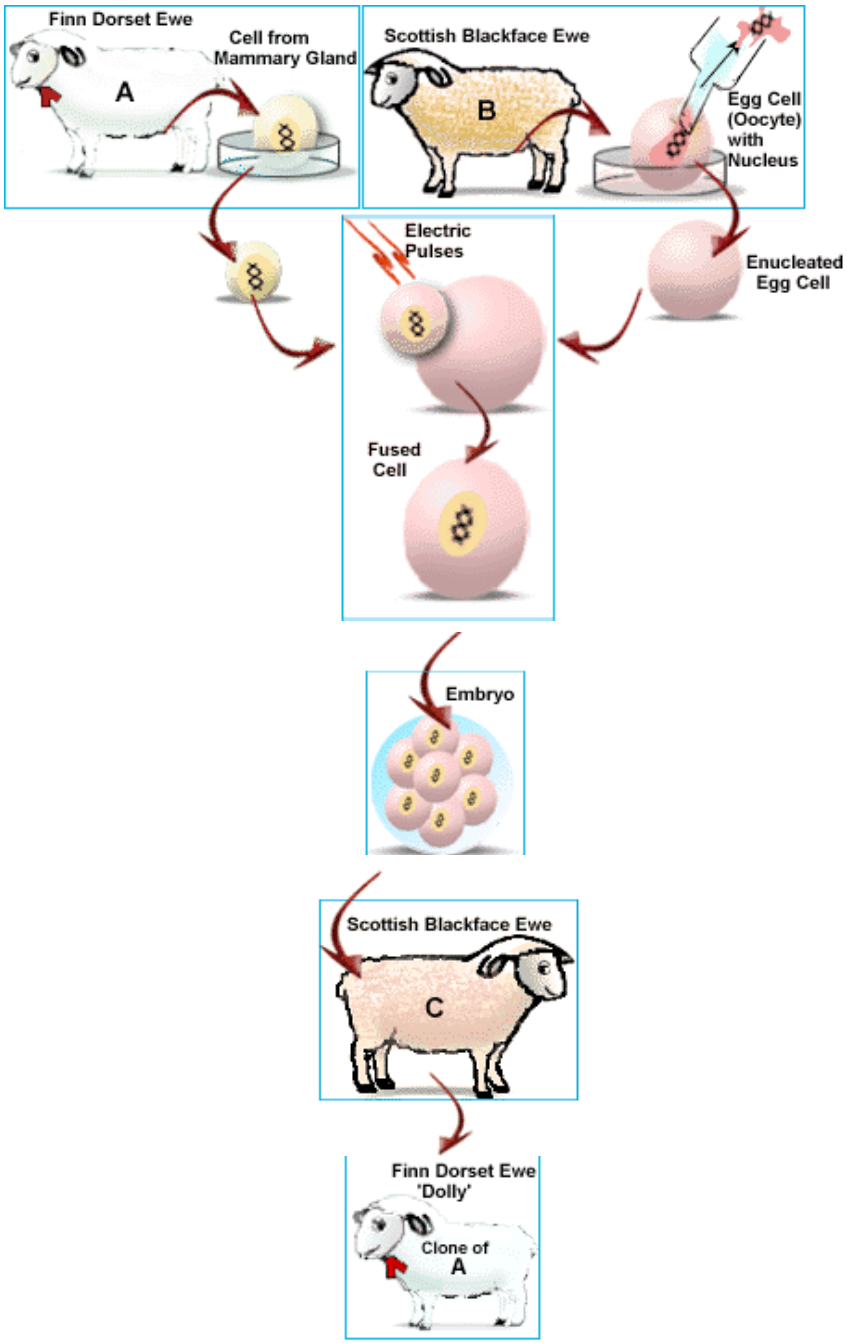




In normal reproduction

- Sperm and oocytes retain telomere length due to the activity of telomerase

- The offspring will have the same length telomeres as the parents



Nucleus removed From egg cell

Cell with DNA fused Into enucleated egg cell

Implantation into The surrogate mother

Birth of clone of Sheep A (Dolly)

Although the clone of sheep A (Dolly) could have been created using only sheep A, sheep B and C were used in the cloning process in order to ensure that Dolly was truly a clone and the not the result of unexpected mating.

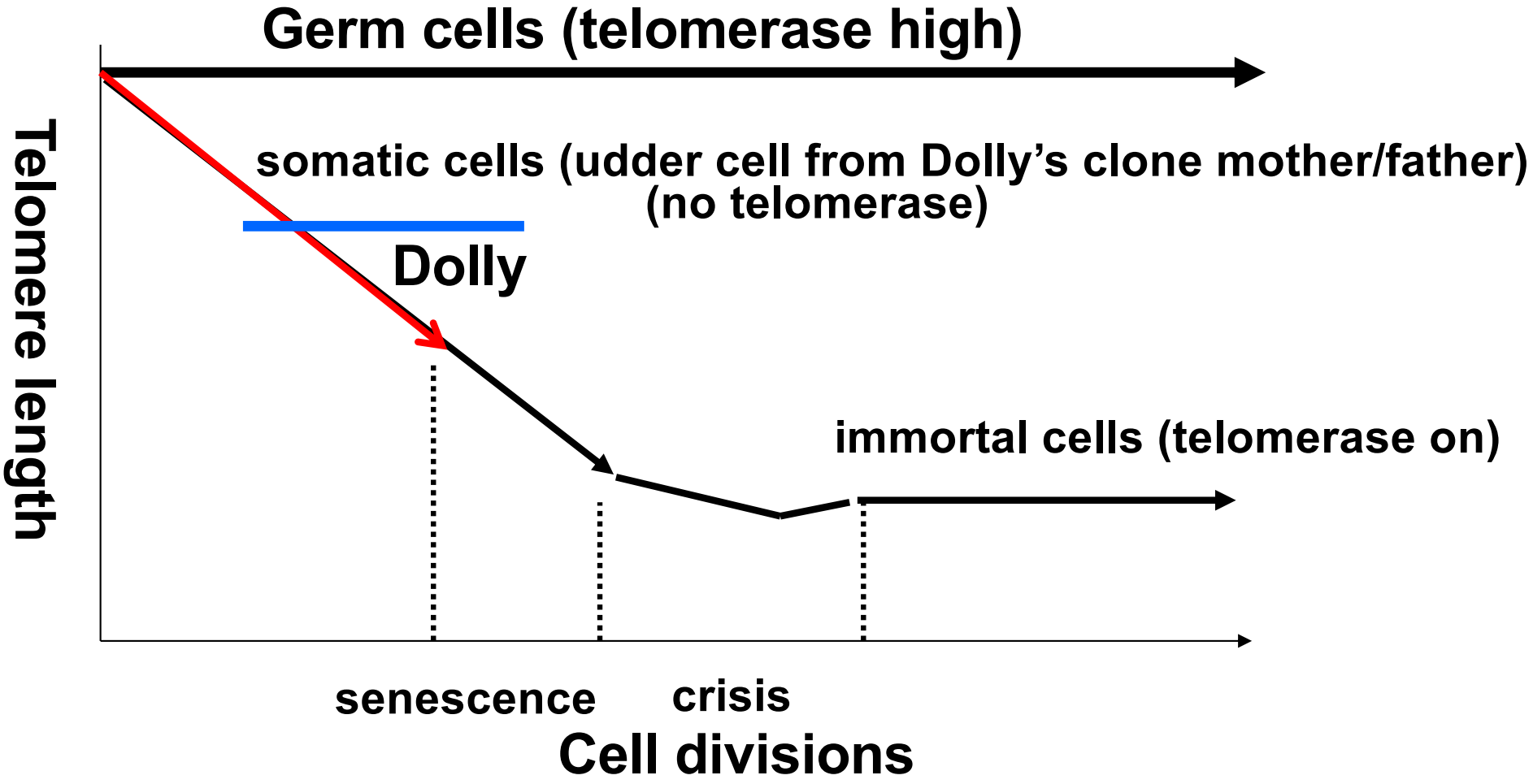
In cloned animals

- Oocytes are enucleated

- Donor cells are somatic cells. No telomerase activity is present.

- Shorter telomere length in these somatic cells compared to sperm/oocyte

What is Dolly's age?



Telomere length of cells in Dolly?

- Comparable to that of a six year older control (sheep live to be about 12 normally) **Nature 399:316-317**

News focus

Death of Dolly marks cloning milestone

Dolly the cloned sheep marked both an icon of scientific possibility and a potential ethical nightmare. Researchers in related fields of stem cell research need to learn the lessons and the right vocabulary if they are to make progress in their fields. Nigel Williams reports.

Dolly the sheep, the world's first mammal to be cloned from an adult cell was put to sleep last month. She was only six and a half years old – barely 40 in human terms. Already being treated for arthritis, Dolly was found to be suffering from a progressive lung disease.

The premature death of Dolly supports the view of some scientists in Japan and the US who maintain that all cloned animals are born with health problems. Harry Griffin, spokesperson for the Roslin Institute, near Edinburgh, where Dolly was created, was cautious on the significance of the ewe's death. 'Sheep can live to 11 or 12 years,' he said. 'Lung infections are common in older sheep, particularly those housed inside. A full postmortem is being conducted and we will report any significant findings.' After the postmortem examination, Dolly will be stuffed and put on display at the National Museum of Scotland.

Dolly was born on July 5 1996, from three mothers: one ewe to provide the DNA, another to provide the egg into which the DNA was injected, and a third to carry the resulting cloned embryo to term. Dolly's genetic mother (the DNA was taken from an udder cell) was six when she was cloned. This may mean that the real age of clones is their age since birth, plus the age of the genetic donor.

The revelation to the world of Dolly's existence, in 1997, was the scientific sensation of the decade. Scientific orthodoxy declared that cloning mammals was impossible: here was the proof. A frenzy of speculation followed about what cloning could achieve. But it is now known that cloning is difficult, expensive and dangerous for the animals involved. Claims of cloned humans remain unproven.

Speculation about its potential came quickly back to earth with the announcement that Dolly had

Goodbye Dolly: The creation of a cloned sheep caused a media sensation but her death demands a rethink of attitudes and presentation of cloning and related stem cell research. (Picture: Science Photo Library.)

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ARTICLE

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Healthy ageing of cloned sheep

K.D. Sinclair[1], S.A. Corr[1], C.G. Gutierrez[1,2], P.A. Fisher[1], J.-H. Lee[1,†], A.J. Rathbone[1], I. Choi[1,†], K.H.S. Campbell[1,✠] & D.S. Gardner[1]

Figure 1 | Four 8-year old Finn-Dorset clones born in July 2007 and derived from the mammary-gland cell line that gave rise to Dolly.

Genex Cooperative Inc News

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A Legend Passes

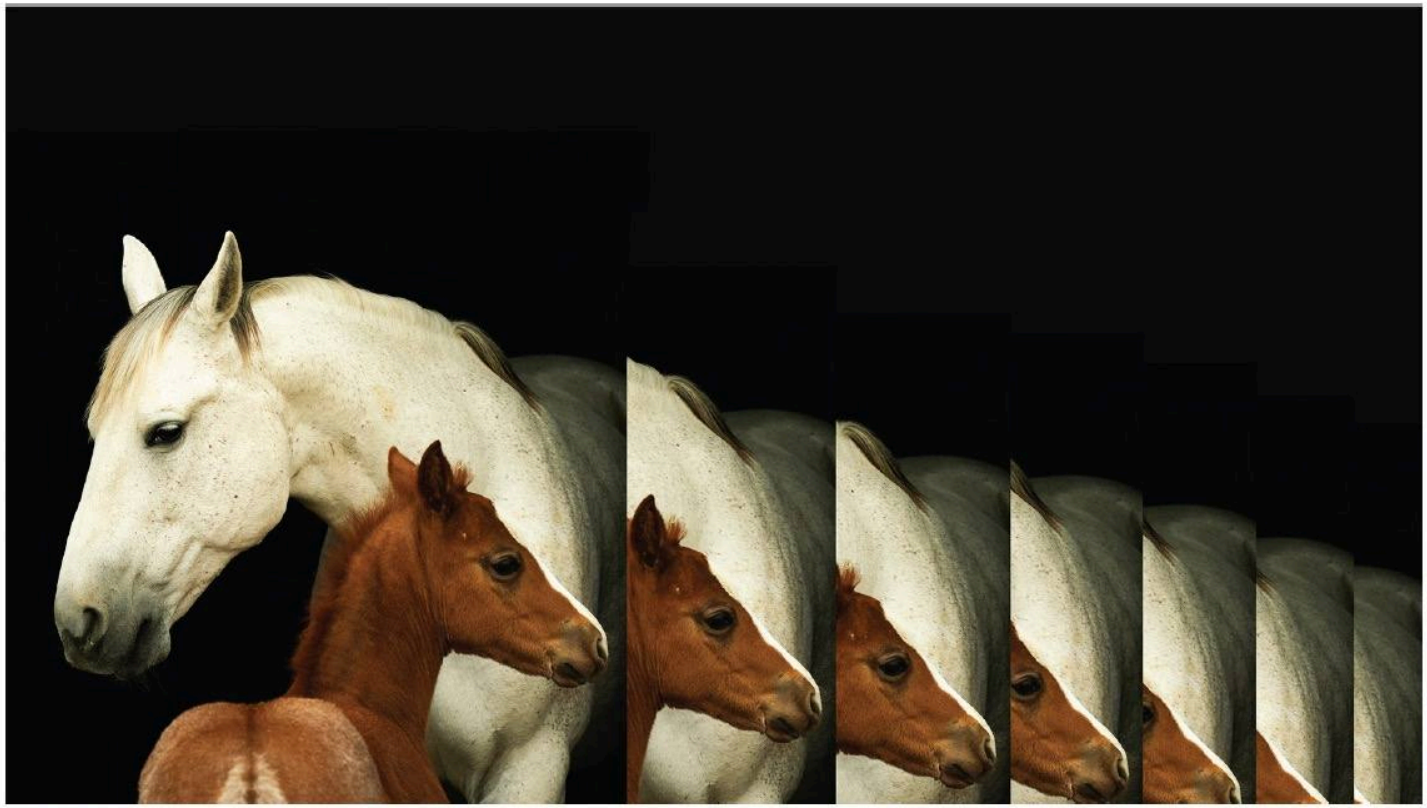
SHAWANO, Wis. – 1AN01044 S A V **FINAL ANSWER** 0035, at 14 years of age, has passed away. Born on February 22, 2000, he sold in the 2001 Martin and Angie Schaff Complete Retirement Dispersal. Genex acquired FINAL ANSWER in 2002. Since then, he has become the highest selling beef sire in the history of Genex.

Since 2009, FINAL ANSWER has been on the top 10 list for Angus registrations every year, ranking as the number one sire for registrations at the end of fiscal year 2012. He currently has 28,712 progeny registered with the American Angus Association along with countless commercial offspring. FINAL ANSWER achieved a great feat for any beef sire, by producing his 500,000th unit of semen on July 25, 2013.

He has attained many notable accomplishments, due in part to his commercial acceptability and extensive use worldwide. He leaves behind moderate, efficient replacement females and superior sons, such as 1AN01146 RIGHT ANSWER, 1AN01222 PRIORITY and 1AN01141 PIONEER. In addition, his legacy continues in his clone, 1AN01259 FINAL ANSWER II, a sire that can be used with the same expectations as FINAL ANSWER.

“I have had the opportunity to work with some of the greatest maternal sires of the breed,” states Willie Altenburg, Genex Associate Vice President of Beef Genetics. “Among that group of iconic sires is Final Answer, he will go down in history as one of the greatest calving ease and maternal sires of his era.”

About Genex
Genex Cooperative, Inc., headquartered in Shawano, Wisconsin, is the trusted provider of world-class animal genetics, progressive reproductive solutions, value-added products and innovative services to members and customers across the U.S. This is accomplished through 950 dedicated employees working in three product and service segments: cattle genetics and reproduction, livestock marketing, and milking and farmstead equipment. Genex is a subsidiary of Cooperative Resources International. Learn more at http://genex.crinet.com.



IDEAS

INSIDE THE BIG BUSINESS OF CLONING ANIMALS

Faster horses, superior cattle, immortal pets

By Bianca Bosker

Photographs by Brian Finke