家畜細胞遺傳

朱有田

References:

1. Lodish et al. 2000. Molecular cell biology (4th edition). W. H. Freeman and company. New York.
2. Hartwell et al. 2000. Genetics: from genes to genomes. McGraw-Hill co. New York.
3. Robertson. 1987. Teratocarcinomas and embryonic stem cells. IRL Press. Oxford. England.
4. Rooney. 2001. Human cytogenetics: constitutional analysis. Oxford university press. New York

Dolly

(a) Dolly

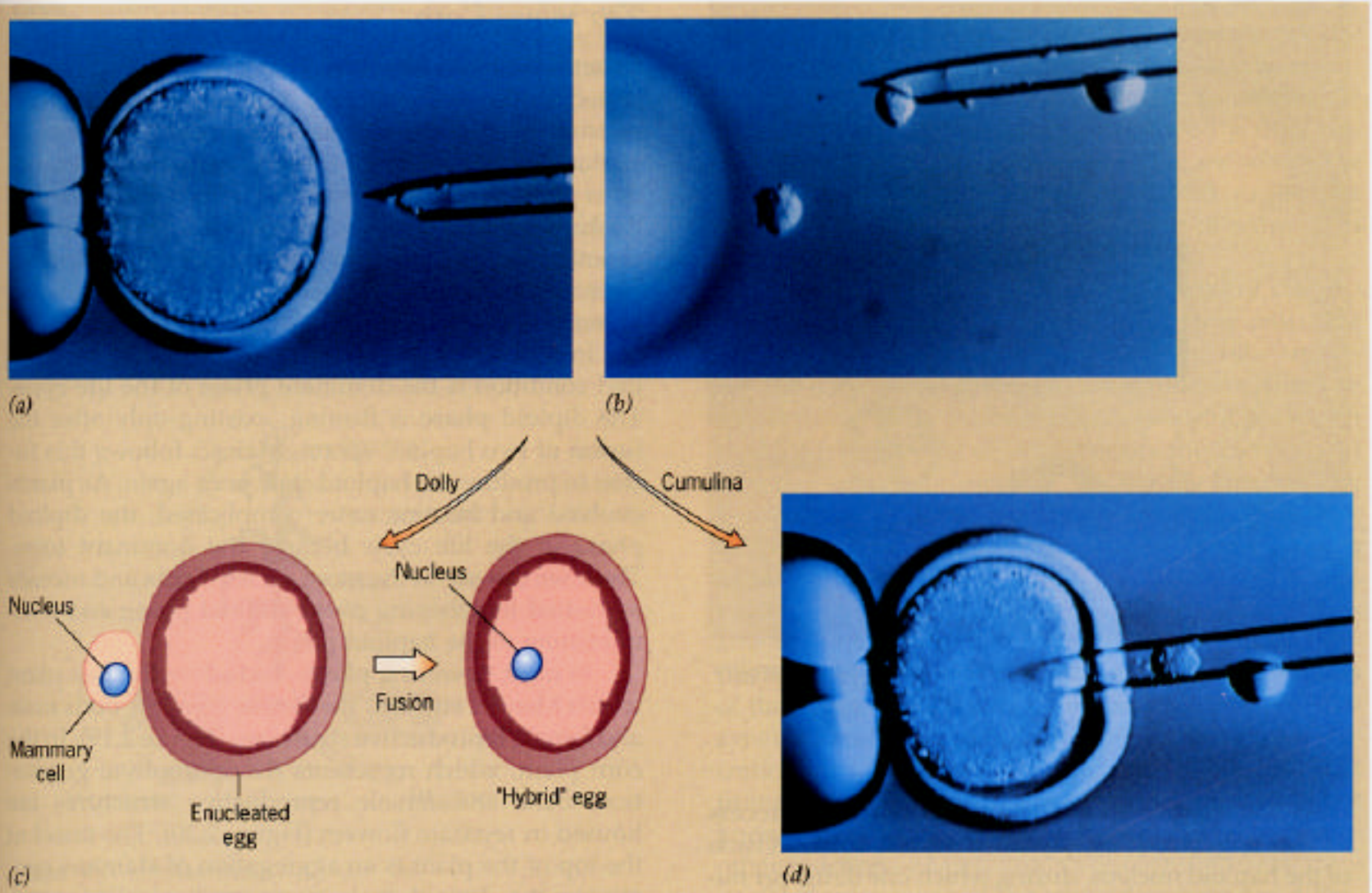


Figure 2 The nuclear transfer techniques used to produce Dolly and Cumulina. In both cases, an egg was enucleated by (*a*) holding it on the tip of a pipette with light suction and (*b*) withdrawing its nucleus with a glass needle. In Dolly's case, (*c*) a short pulse of electricity was used to fuse the enucleated egg with a mature mammary cell. To produce Cumulina, (*d*) scientists used a glass needle to inject a nucleus removed from a cell of an adult mouse into the enucleated egg. In both cases, the nucleated eggs were grown briefly in embryo culture before being implanted in surrogate mothers.

Dollay and cal

Classical Genetics = Gregor Mendel (1865)

1: Simple organism: garden pea

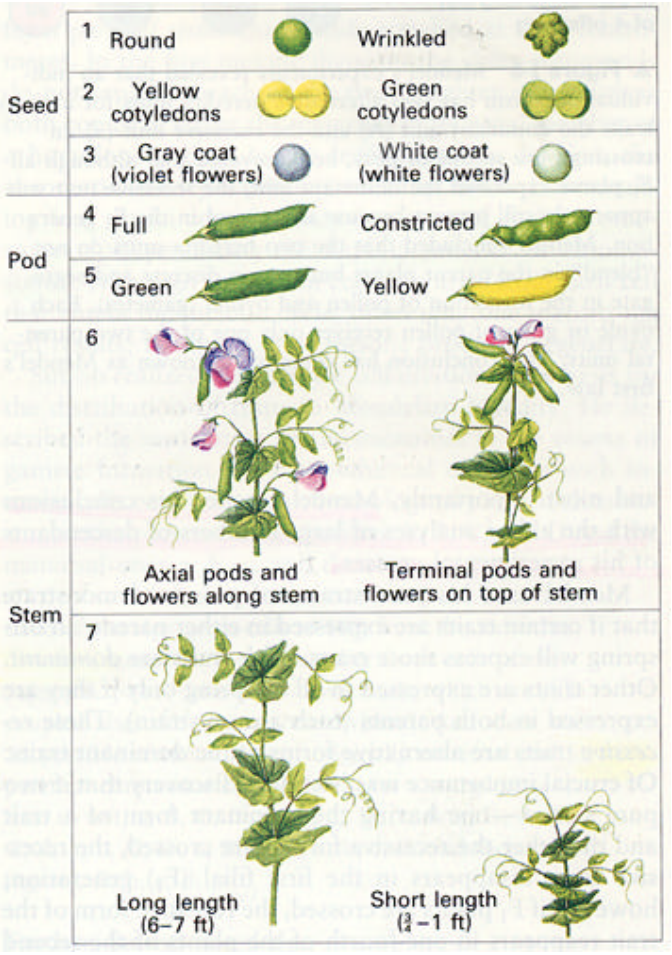
2: Repeat self-pollination … Bred true

3: The trait could be determined unambiguously

4. Analysis of large number of descendant of his experimental crosses

Dominant and Recessive

▲ **Figure I-4** Gregor Mendel (1822–1884), the father of genetics. *Courtesy of the Moravian Museum, Brno.*

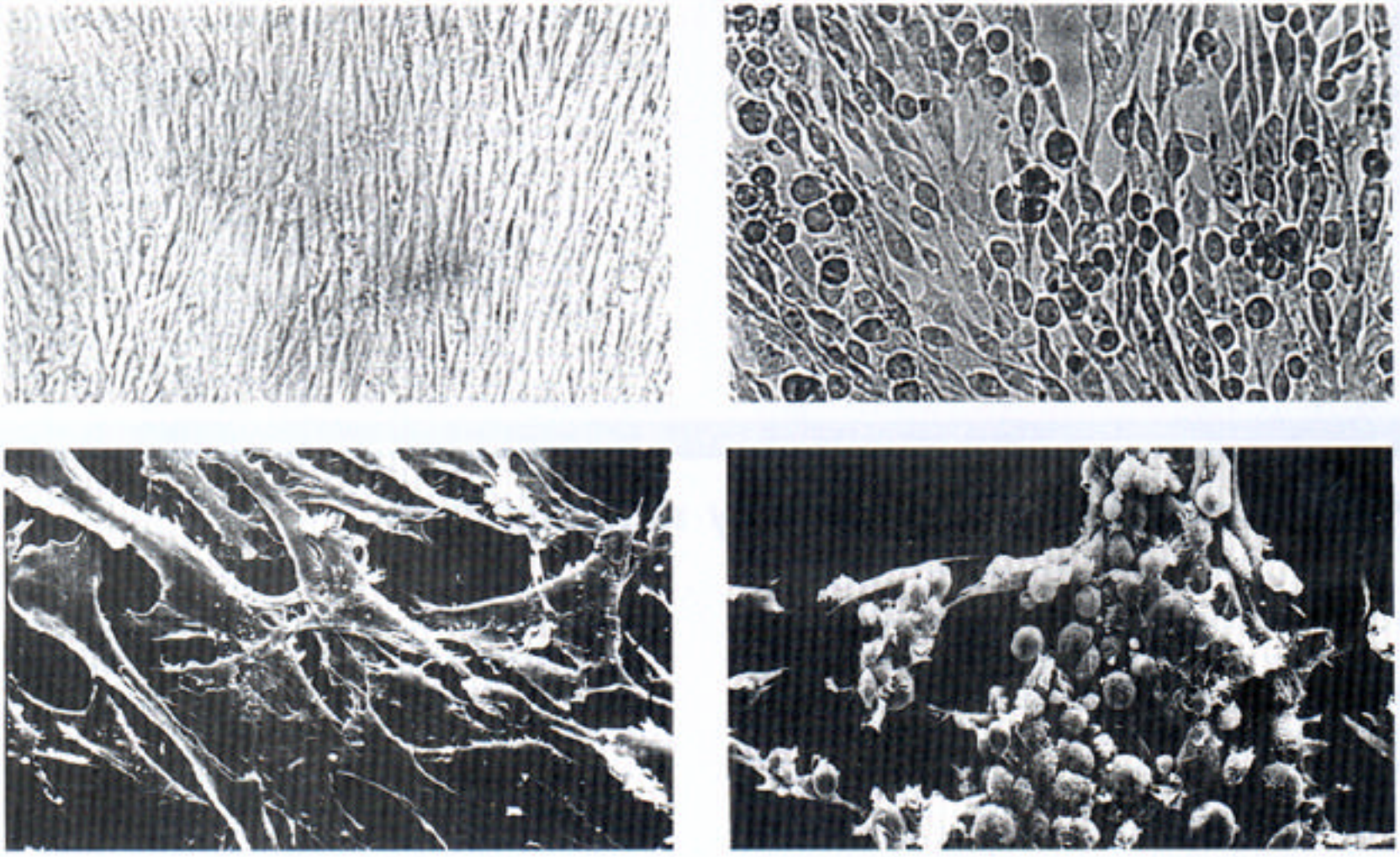


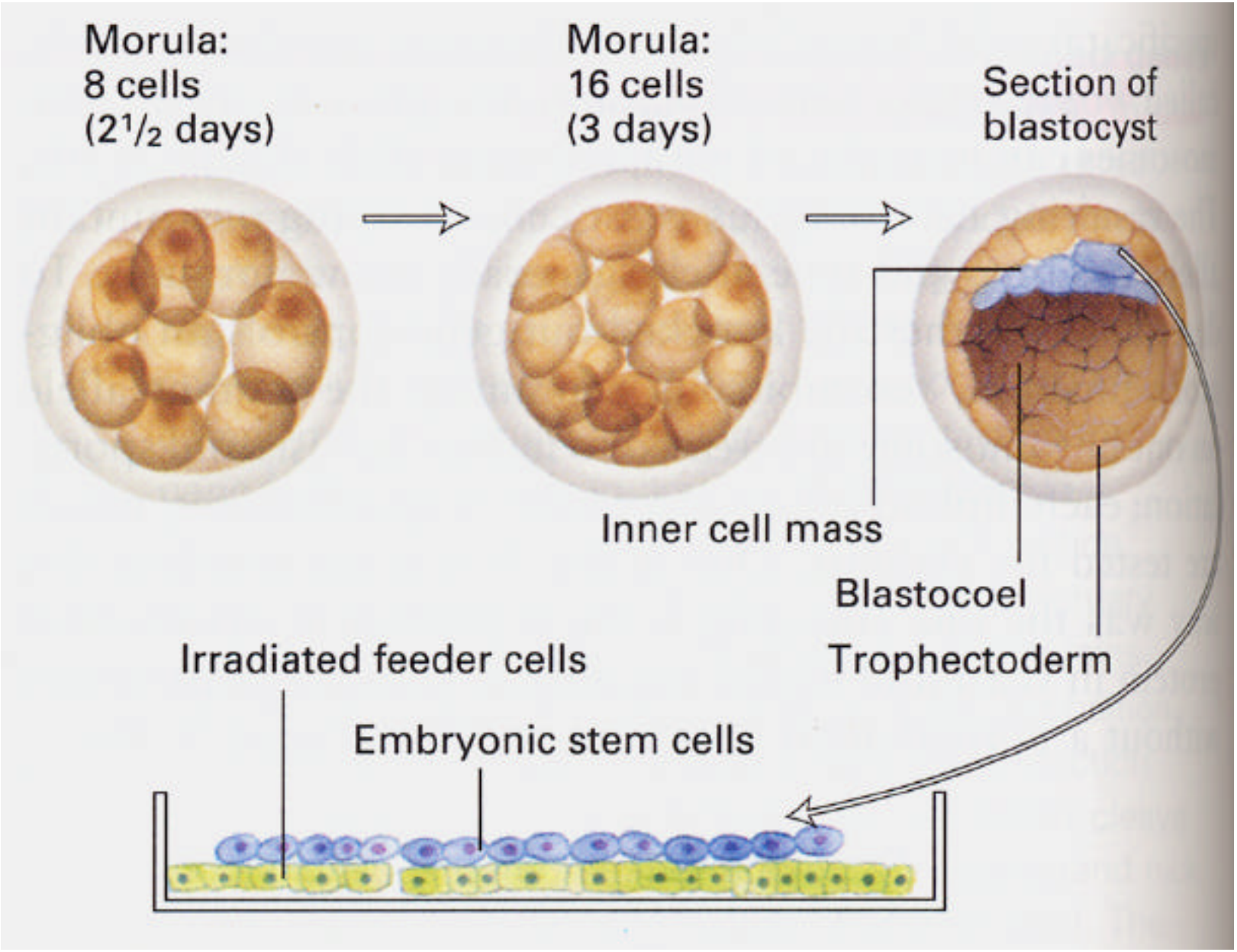
▲ **Figure I-12** (*left*) James D. Watson (1928–) and (*right*) Francis H. C. Crick (1916–) with the double-helical model of DNA they constructed in 1952–1953. *From J. D. Watson,* The Double Helix, *Atheneum, p. 215, copyright 1968 by J. D. Watson. Courtesy of A. C. Barrington Brown.*

Checkpoint

Tumor formation

Figure 28.2 Normal fibroblasts grow as a layer of flat, spread-out cells, whereas transformed fibroblasts are rounded up and grow in cell masses. The cultures on the left contain normal cells, those on the right contain transformed cells. The top views are by conventional microscopy, the bottom by scanning electron microscopy. Photographs kindly provided by Hidesaburo Hanafusa and J. Michael Bishop.





1/100-
1/10000

Embryonic stem (ES) cells

The culture of embryonal carcinoma (EC) cells - the stem cells of teratocarcinomas

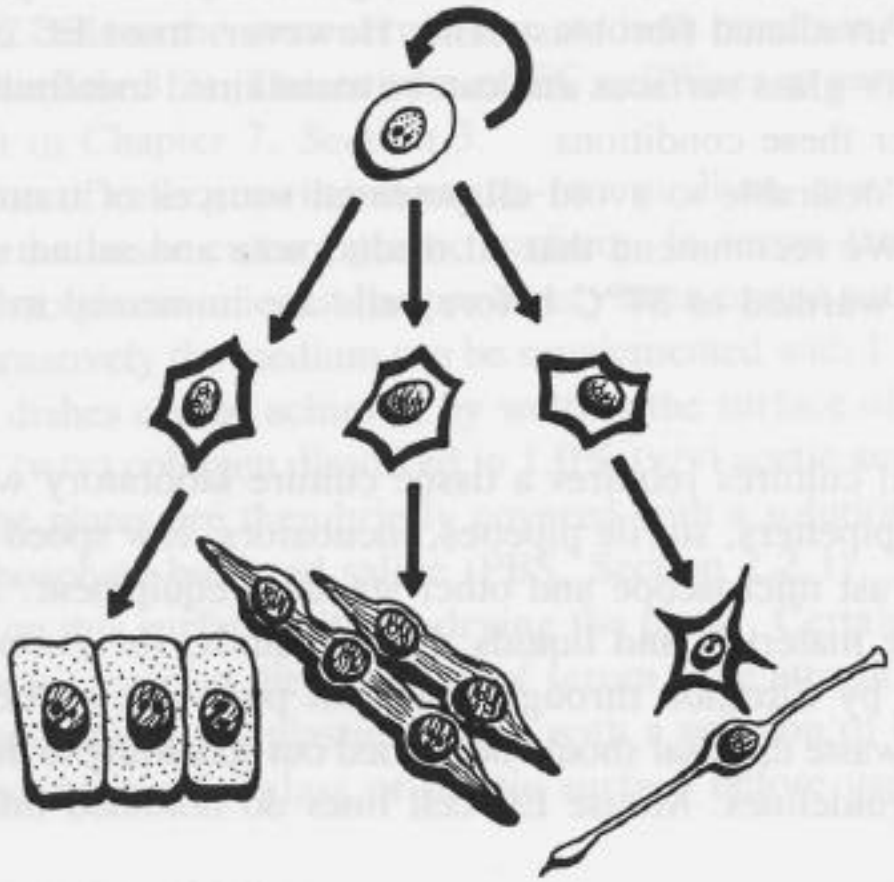


Figure 1. Stem cell model for teratocarcinomas showing the relationship between EC cells and their differentiated derivatives. Shown at the top of the diagram is the EC cell. Its ability for self renewal is indicated by the semicircular line with an arrow. Morphologically undifferentiated but developmentally restricted cells are represented by the second tier of cells and the fully differentiated derivatives of these committed precursors are represented in the bottom row of cells denoting epithelium, skeletal muscle and neurons.

Fluorescence

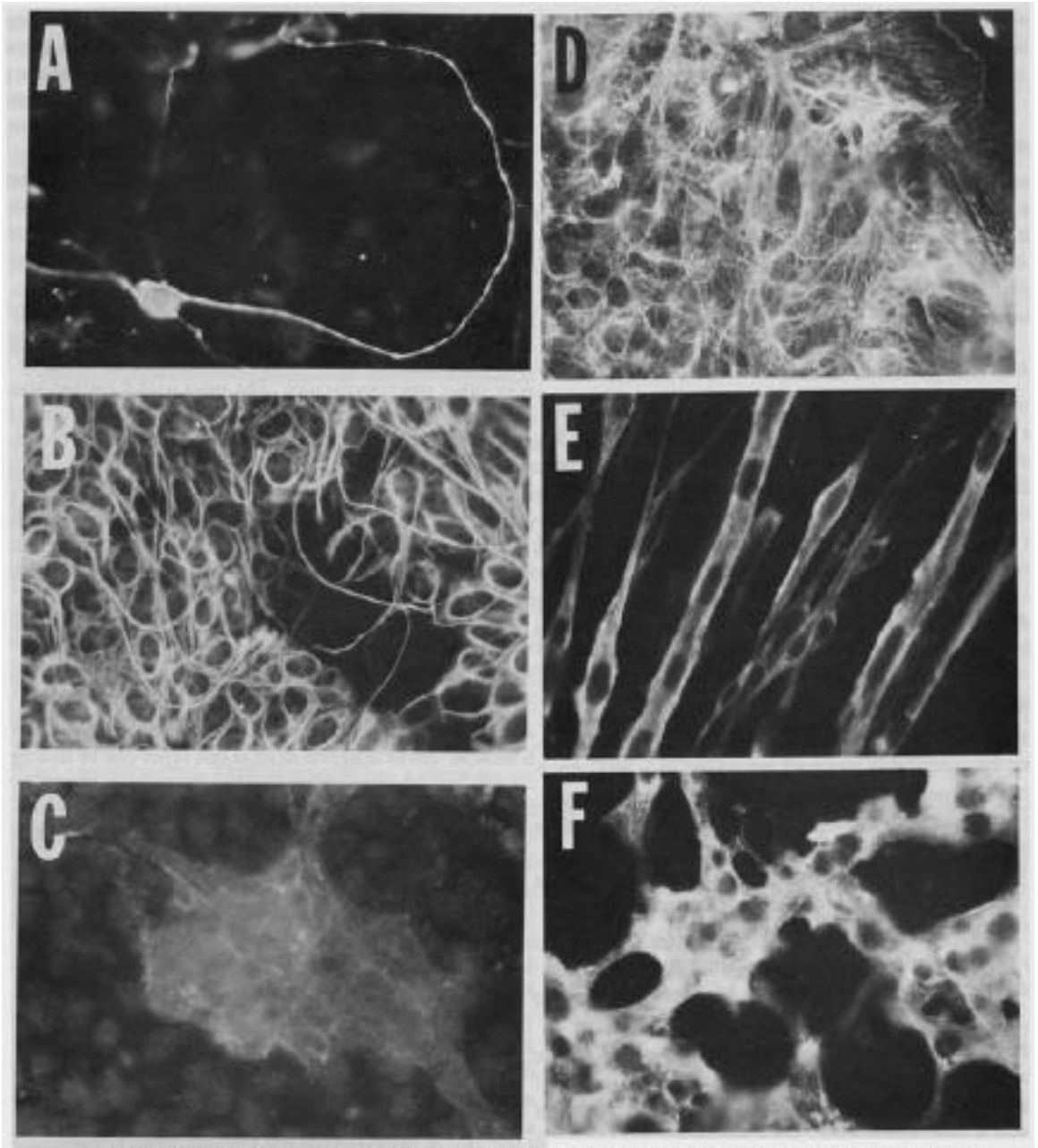
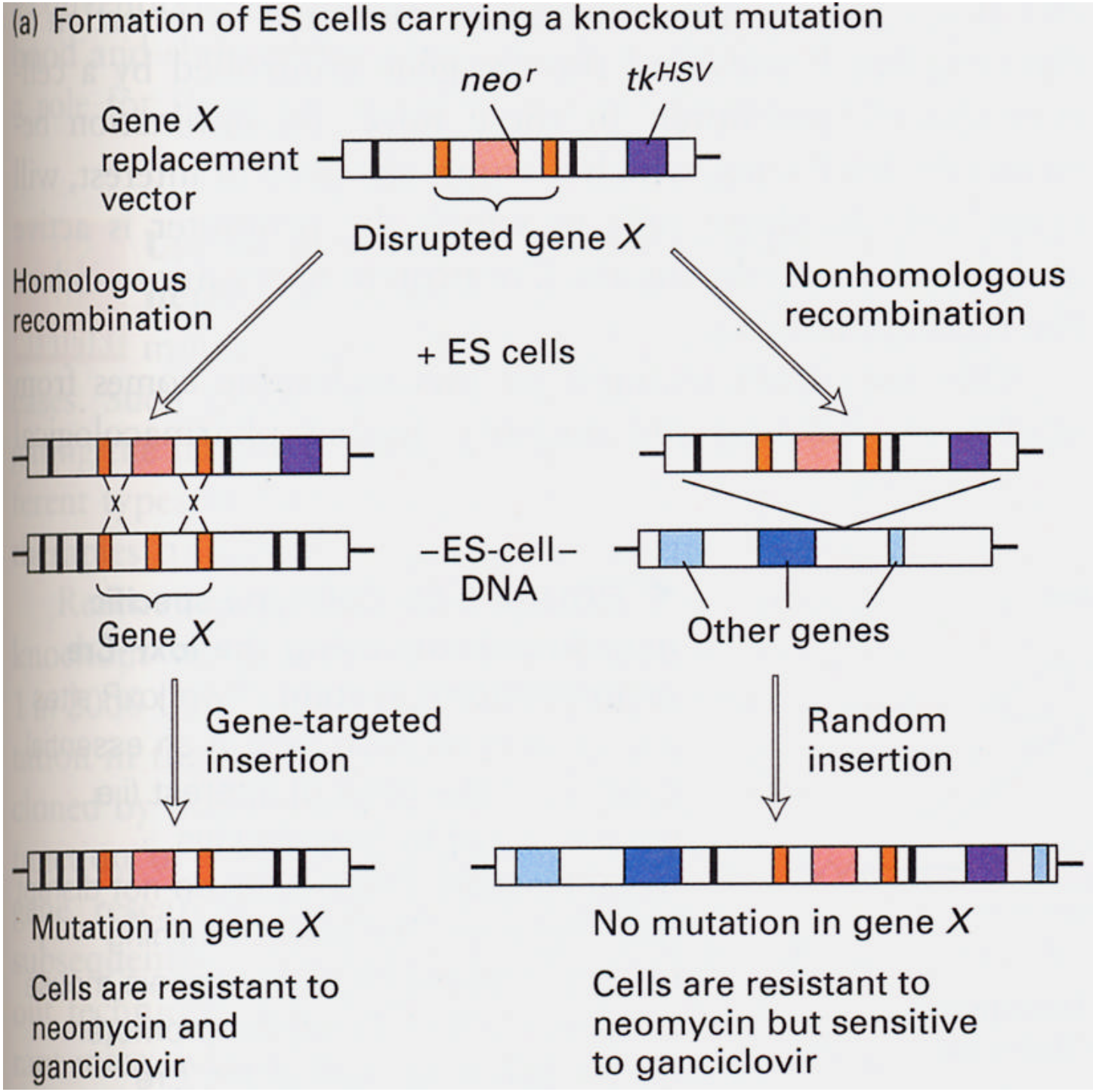
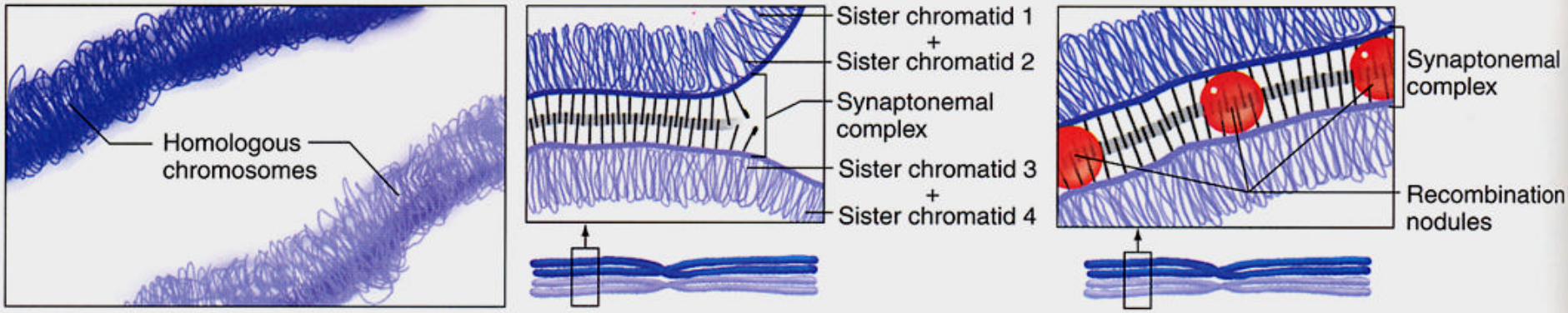


Figure 6. Differentiated cells derived from P19 EC cells identified by staining of lineage-restricted markers by indirect immunofluorescence microscopy. (A) Neuron stained with anti-neurofilament antisera. **(B)** Glia cells stained with anti-glial fibrillar protein antisera. **(C)** Muscle cells stained with anti-sarcomeric α-actin antisera. **(D)** Epithelial cells stained with anti-keratin antisera, Troma-I (30). Skeletal muscle **(E)** and cardiac muscle **(F)** stained with anti-muscle myosin monoclonal antibody, MF20 (31).


(a) Formation of ES cells carrying a knockout mutation
neo^r
tk^HSV
Gene X replacement vector
Disrupted gene X
Homologous recombination
+ ES cells
Nonhomologous recombination
X
X
–ES-cell–DNA
Gene X
Other genes
Gene-targeted insertion
Random insertion
Mutation in gene X
Cells are resistant to neomycin and ganciclovir
No mutation in gene X
Cells are resistant to neomycin but sensitive to ganciclovir

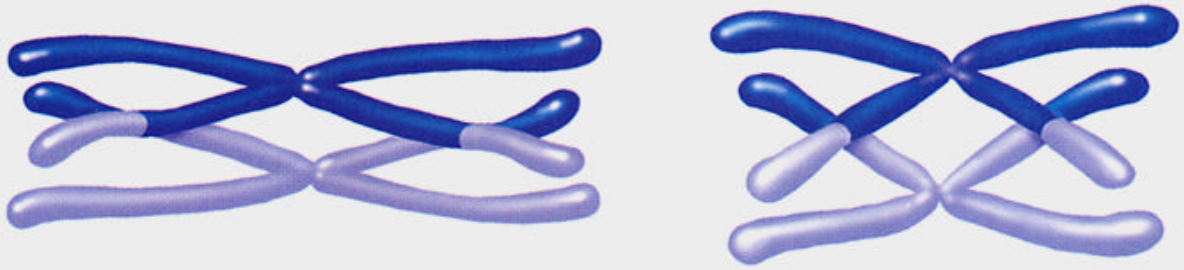
General procedure for producing gene-targeted knockout mice



(a) Leptotene: Threadlike chromosomes begin to condense and thicken, becoming visible as discrete structures. Although the chromosomes have duplicated, the sister chromatids of each chromosome are not yet visible in the microscope.

(b) Zygotene: Chromosomes are clearly visible, and begin active pairing with homologous chromosomes along the synaptonemal complex to form a bivalent, or tetrad.

(c) Pachytene: Full synapsis of homologues. Recombination nodules appear along the synaptonemal complex.



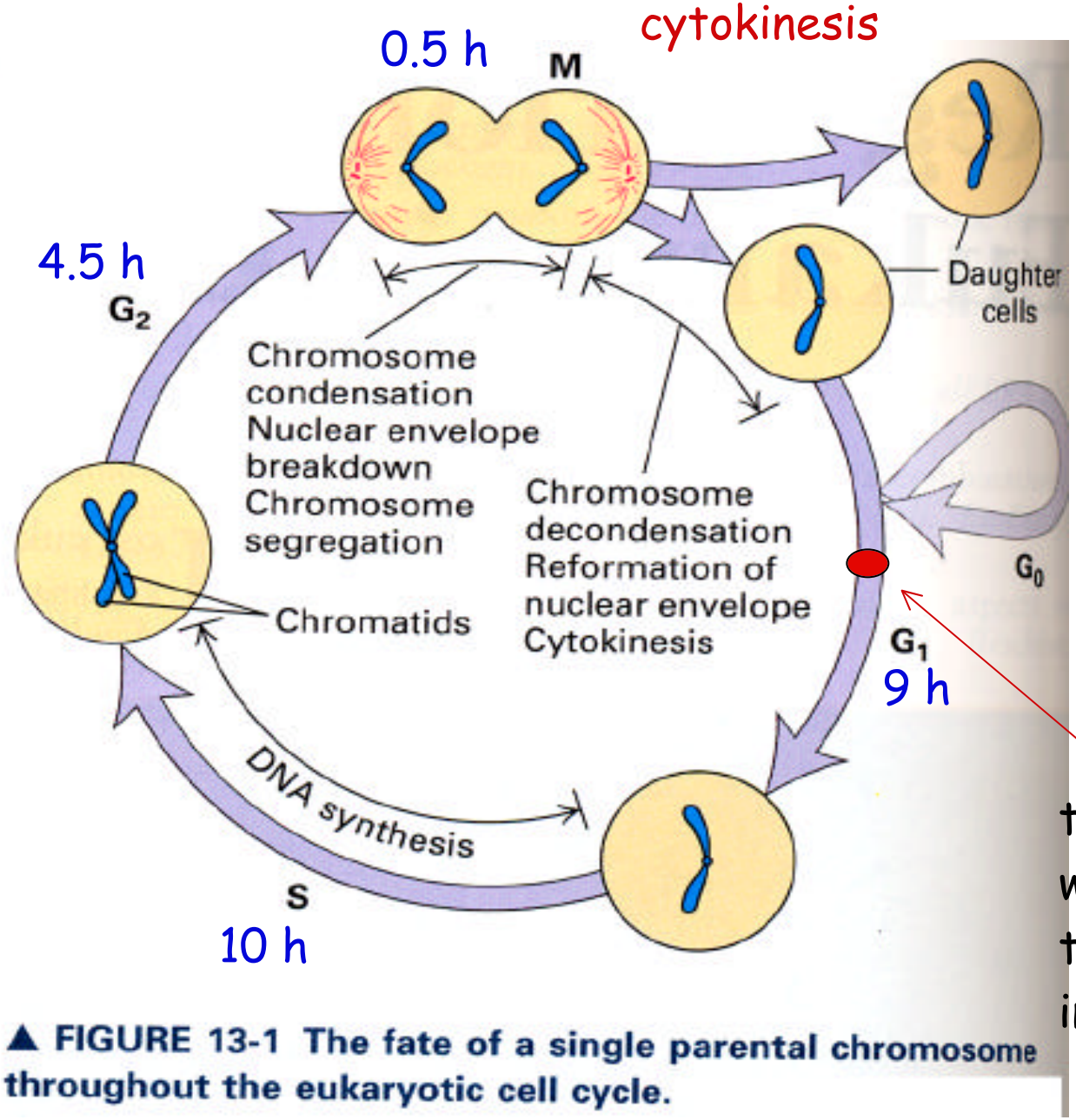
(d) Diplotene: Bivalent appears to pull apart slightly, but remains connected at crossover sites, called chiasmata.

(e) Diakinesis: Further condensation of chromatids. Nonsister chromatids that have exchanged parts by crossing-over remain closely associated at chiasmata.

Figure 3.14 Prophase I of meiosis at very high magnification.

Dolly

(a) Dolly



▲ FIGURE 13-1 The fate of a single parental chromosome throughout the eukaryotic cell cycle.

Postmitotic cells:

"exit" the cell cycle

G_0 ------ Neuron

Restriction point

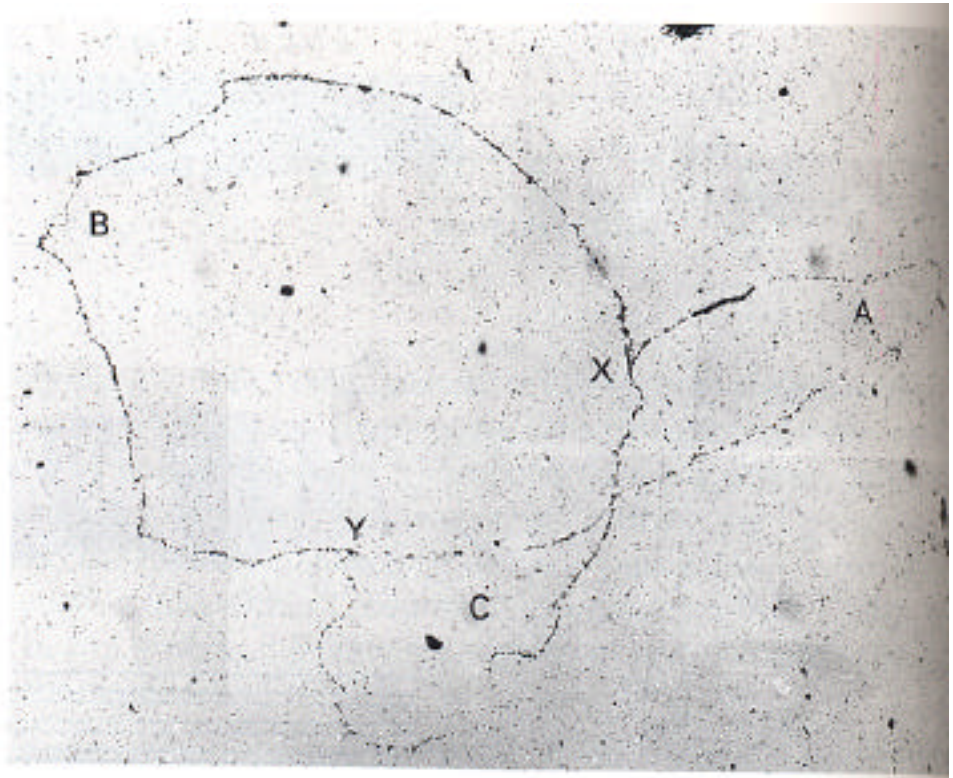
the point in late G1 where passage through the cell cycle become independent of mitogens

Most bacterial chromosome are circular with one replication origion

1. Charge repulsion:
   spermine and spermidine
   (polyamines)

2. Small protein (H-NS =15.6 kDa)

3. Tightly supercoiled



▲ **FIGURE 9-27 Autoradiograph of the *E. coli* chromosome labeled with [^{3}H]-thymine.** Points X and Y indicate the positions of DNA replication forks. Region B is the unreplicated parental chromosome. Regions A and C are the newly replicated nascent daughter chromosomes containing one parental strand and one newly replicated daughter strand. [From J. Cairns, 1964, *Cold Spring Harbor Symp. Quant. Biol.* **28**:43.]

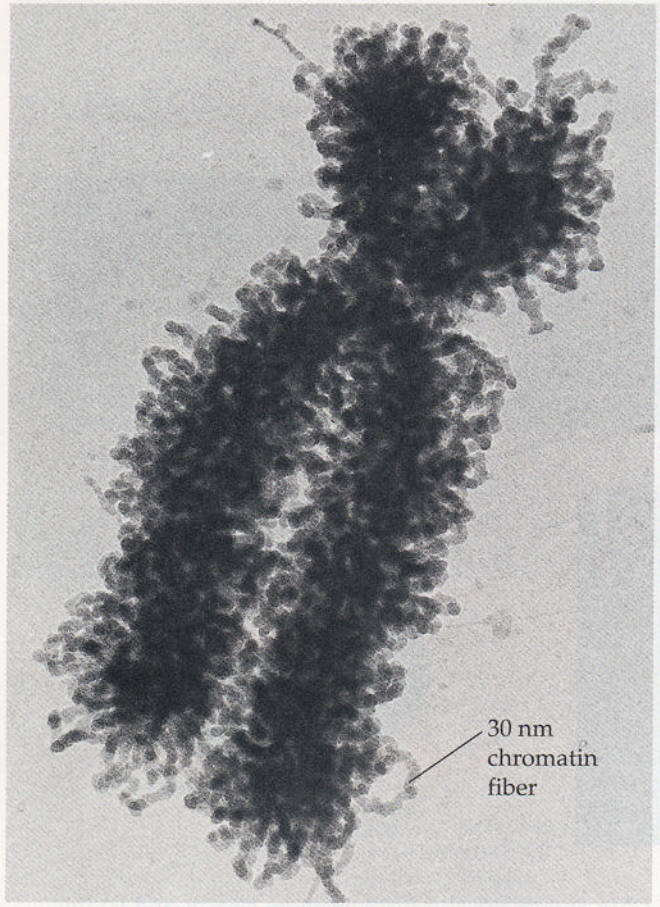


Figure 10.27 Electron micrograph of a human metaphase chromosome showing the presence of 30-nm chromatin fibers. The available evidence indicates that each chromatid contains one large, highly coiled or folded 30-nm fiber.

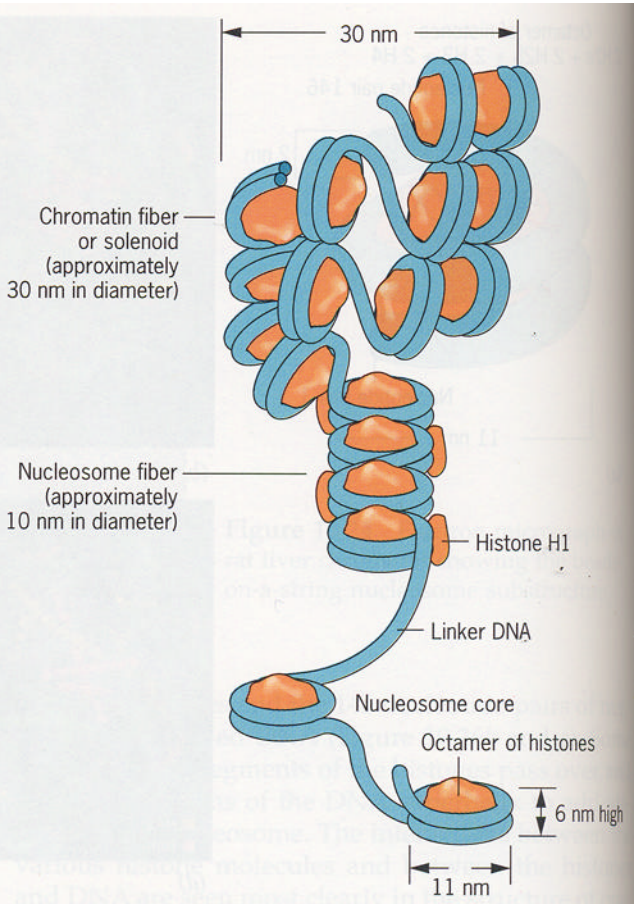


Figure 10.28 Diagram of the solenoid model of the 30-nm chromatin fiber. Histone H1 appears to stabilize the 10-nm nucleosome fiber and contribute to the formation of the 30-nm chromatin fiber.

A, B and Z form DNA

B-DNA (in vivo):
In physiological condition (low salt)

A-DNA (in vivo):
DNA-RNA or RNA-RNA heteroduplexes

Z-DNA (in vitro):
G=C or C=G

Topoisomerase
DNA gyrase

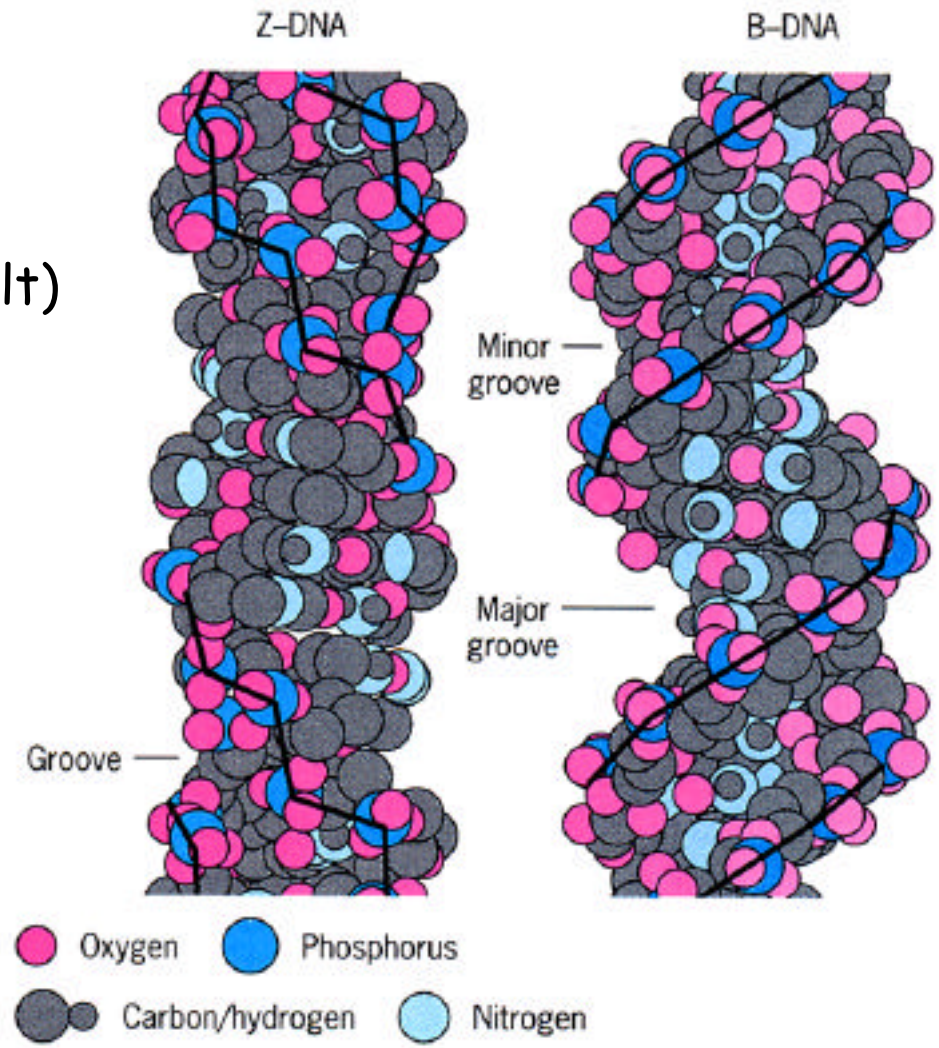


Figure 10.14 Comparison of the structures of Z-DNA and B-DNA. Note the left-handed winding and the zigzagged paths of the sugar-phosphate backbones (solid lines) of the Z-DNA double helix in contrast to the smooth paths and right-handed winding of the backbones in the B-DNA helix.

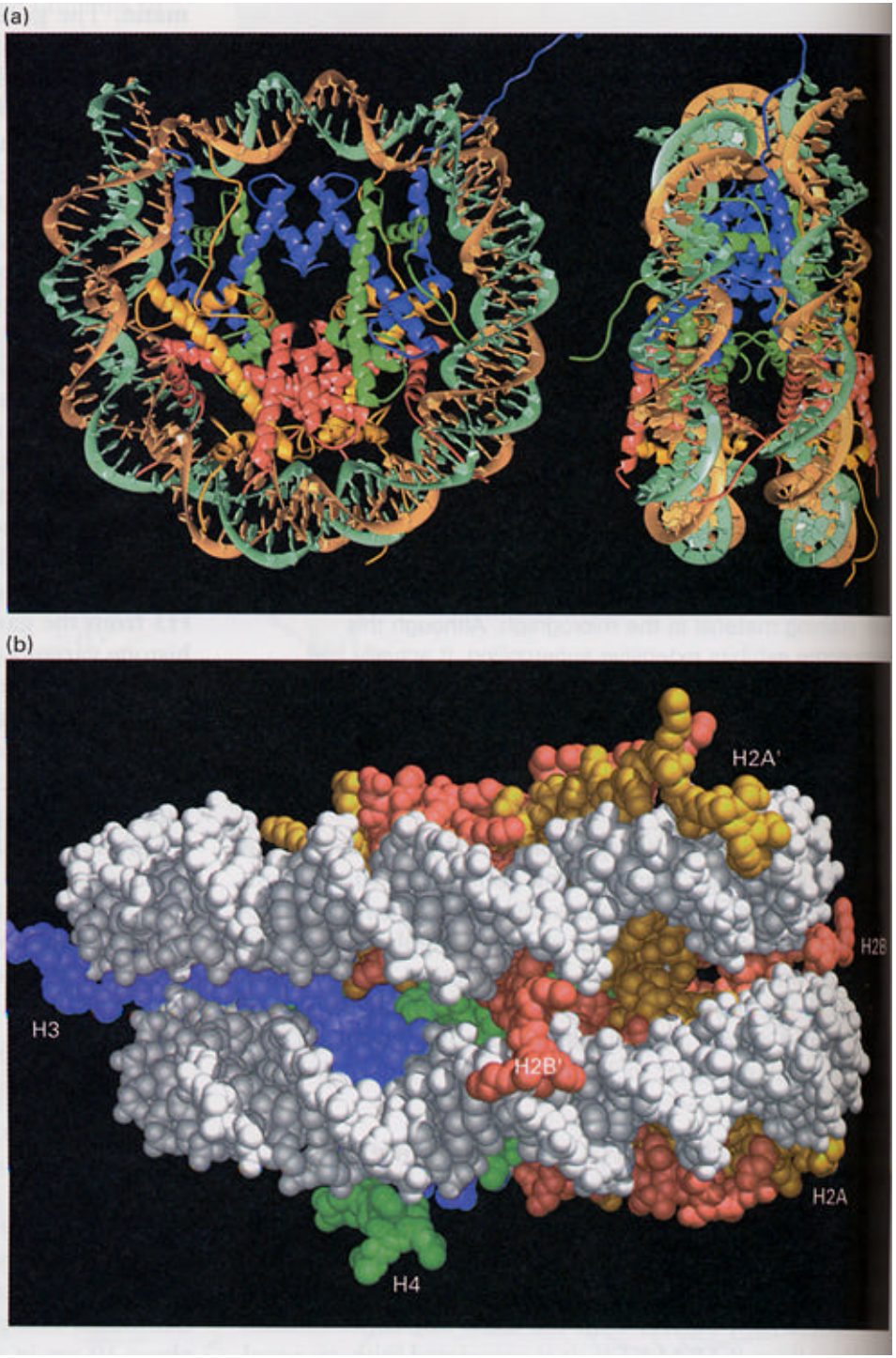
Structure of necleosome

Histone: N-terminal 20-40 residue containing positively charged lysine groups

CH3COO-

Acetylation and deacetylation of specific lysines

▶ **FIGURE 9-30 Structure of the nucleosome.** (a) Ribbon diagram of the nucleosome shown face-on *(left)* and from the side *(right)*. One DNA strand is shown in green and the other in brown. H2A is yellow; H2B, red; H3, blue; H4, green. (b) Space-filling model shown from the side. DNA is shown in white; histones are colored as in (a). H2A, H2A′, H2B, H2B′, H3, and H4 indicate the positions of the respective histone N-terminal tails visible in this view. The H2A′ N-terminal tail interacts with the upper loop of DNA, while the H2A N-terminal tail (only partially seen in this view) interacts with the bottom loop of DNA. The N-terminal tail of one H4 extends from the bottom of the nucleosome and interacts with the neighboring histone octamer in the crystal lattice (not shown). The N-terminal tails of histones H2B, H2B′, H3, and H3′ pass between the two loops of DNA. The N-terminal tails of H2A, H4, H3, and H2B include an additional 3, 15, 19, and 23 residues, respectively, that are not visualized in the crystal structure because they are not highly structured. They extend further from the surface of the nucleosome where they may participate in nucleosome-nucleosome interactions in the 30 nm fiber (See Figure 9-31) or interact with other chromatin-associated proteins. [From K. Luger et al., 1997, *Nature* **389**:251; courtesy of T. J. Richmond.]

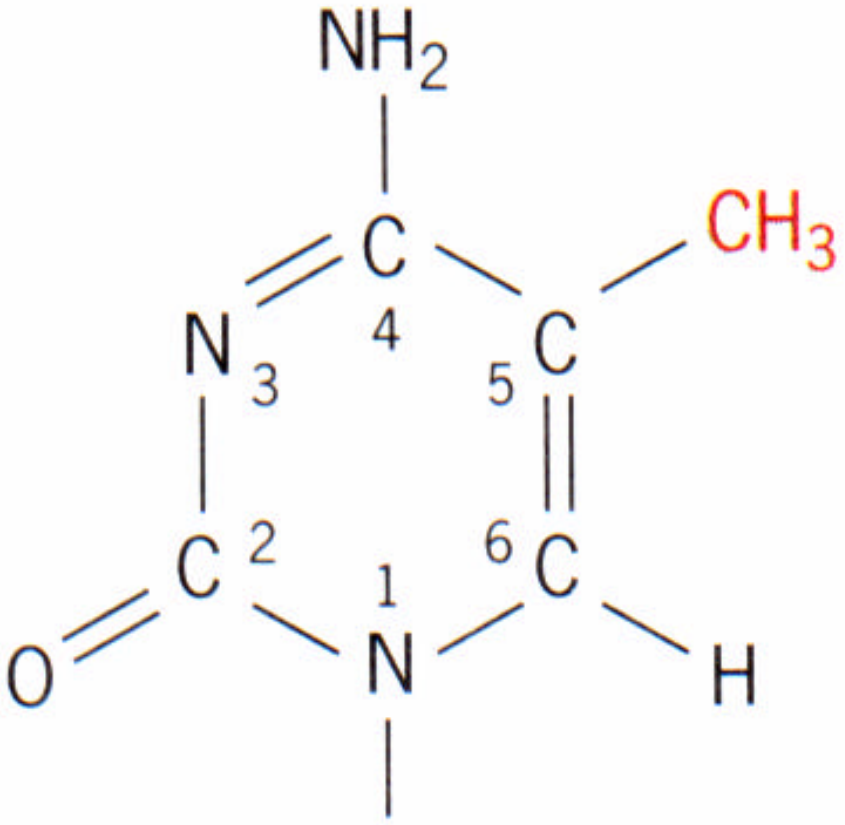


Acetylation of histone N-termini reduces chromatin condensation

Methylation

5′ mC p G 3′
3′ G p Cm 5′

2-7% of C

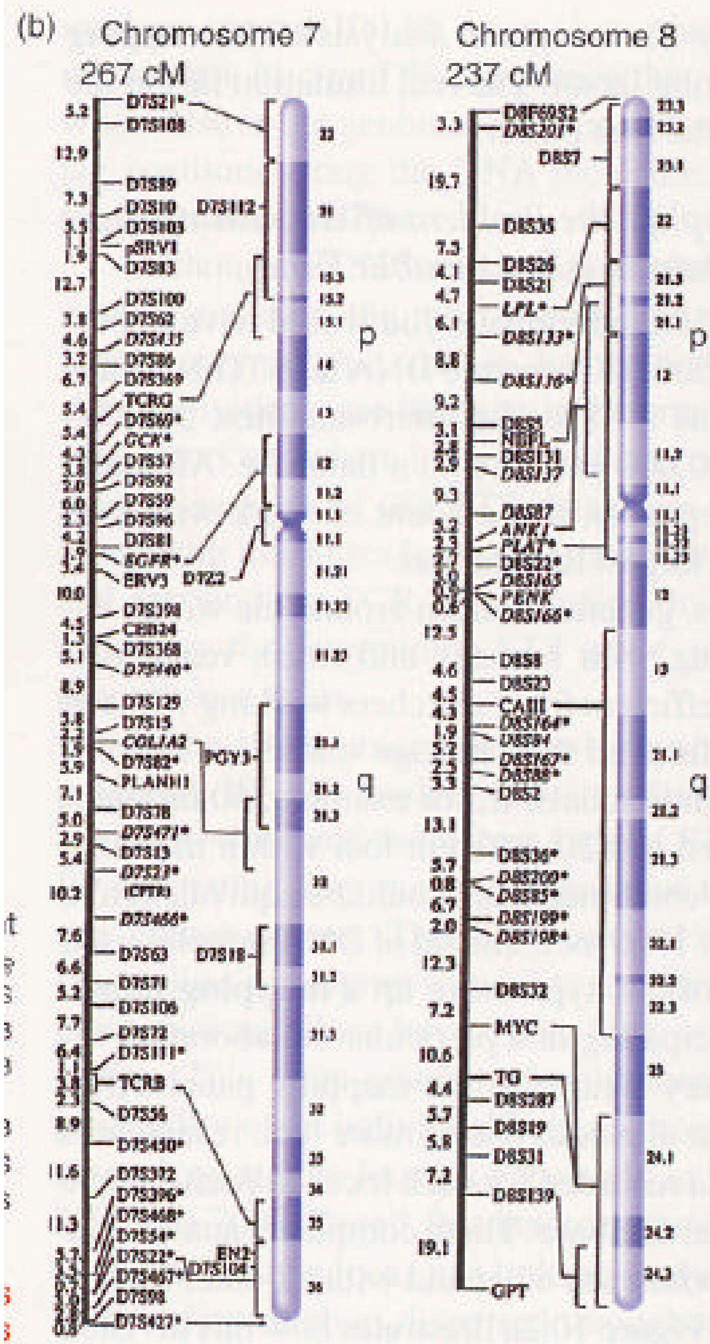


5-methylcytosine

Methylases

Demethylases

The structure of 5-methylcytosine.


(b)
Chromosome 7
267 cM
Chromosome 8
237 cM
p
q
p
q
TCRG
TCRB
MYC
GPT

Banding nomenclature:

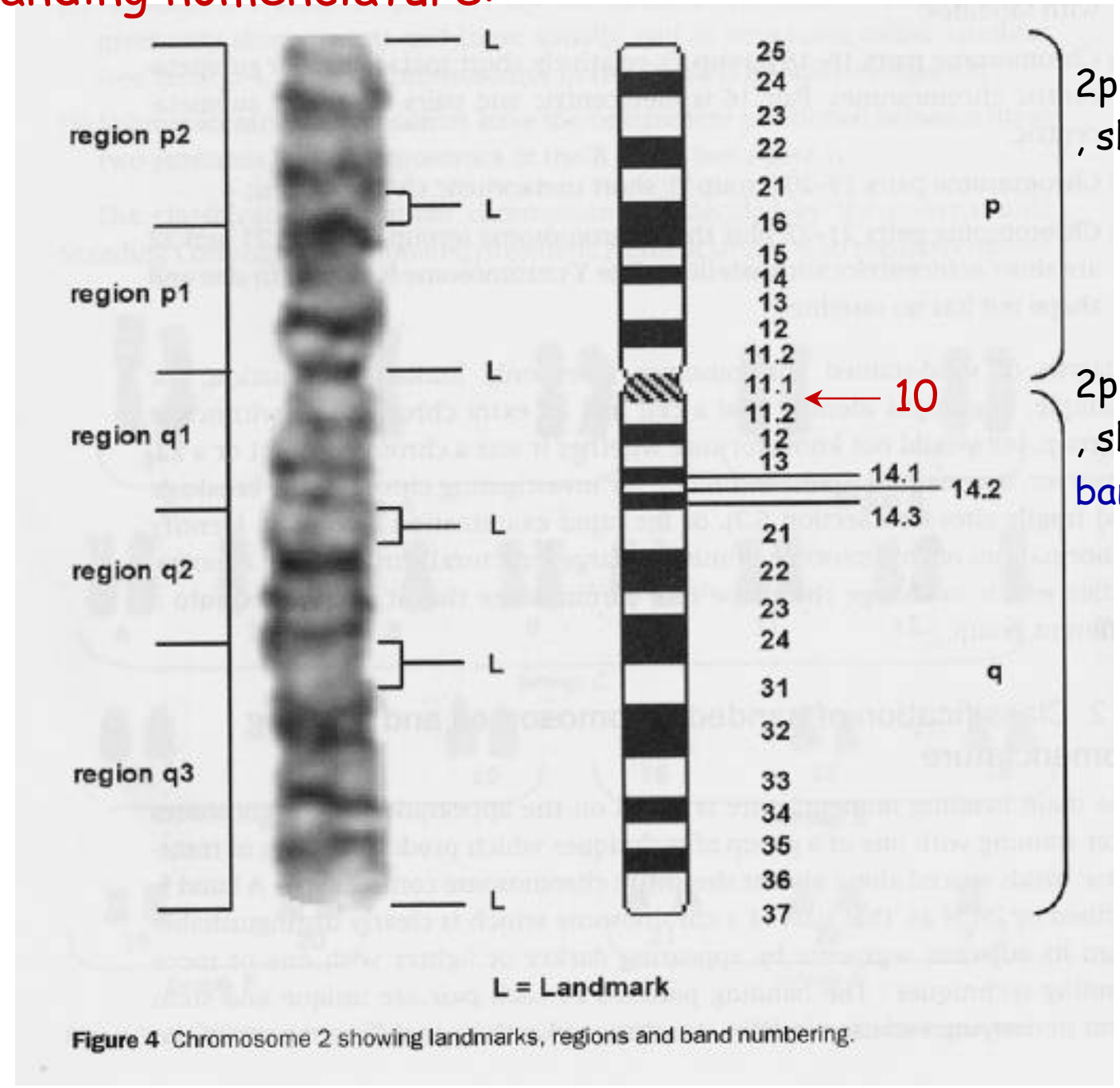


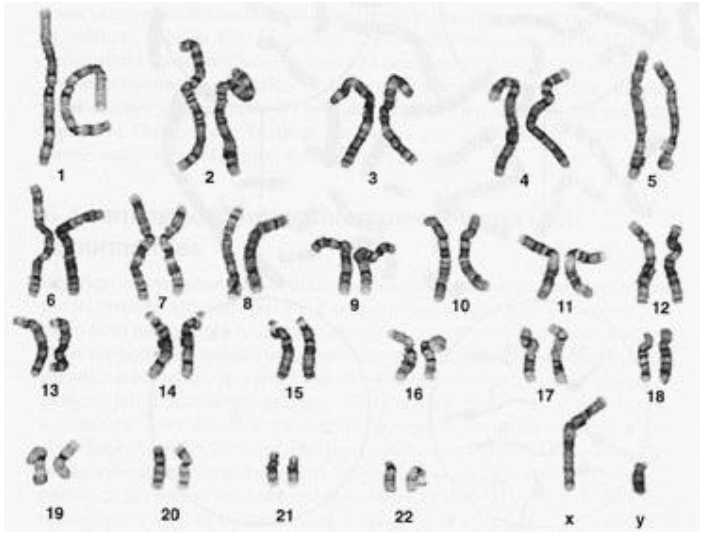
Figure 4 Chromosome 2 showing landmarks, regions and band numbering.

2p2: chromosome 2 , short arm, region 2

2p25: chromosome 2 , short arm, region 2, band 5

Eukaryotic chromosome : Molecular anatomy

1. What is the structure of DNA



2. What form is the genetic information

3. What feature of the structure DNA facilitate the accurate transmission of genetic information from generation to generation

Dosage compensation

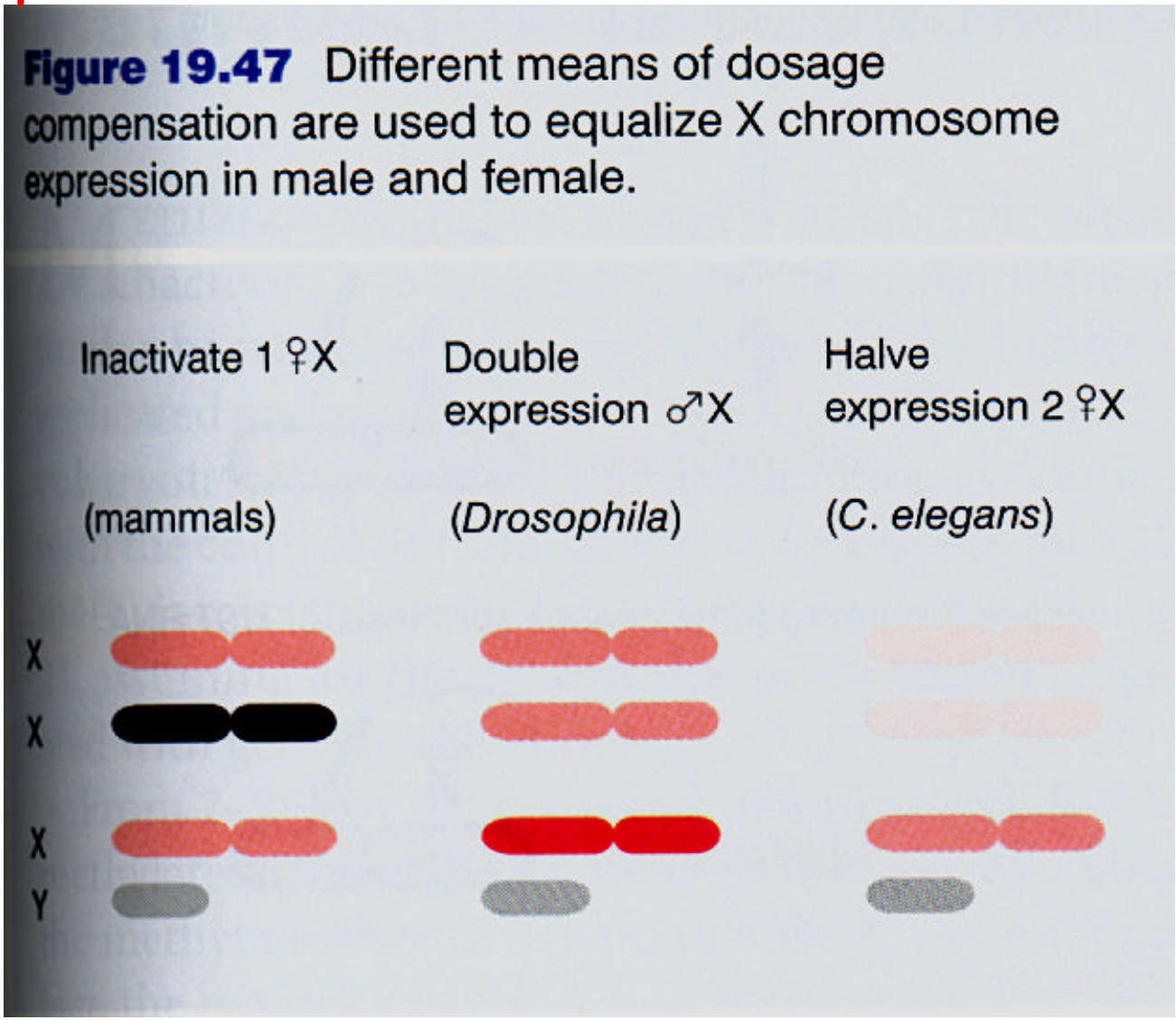


Figure 19.47 Different means of dosage compensation are used to equalize X chromosome expression in male and female.

The entire chromosome is the target for regulation

Constitutive heterochromatin

Facultative heterochromatin

YAC (yeast artificial chromosome)

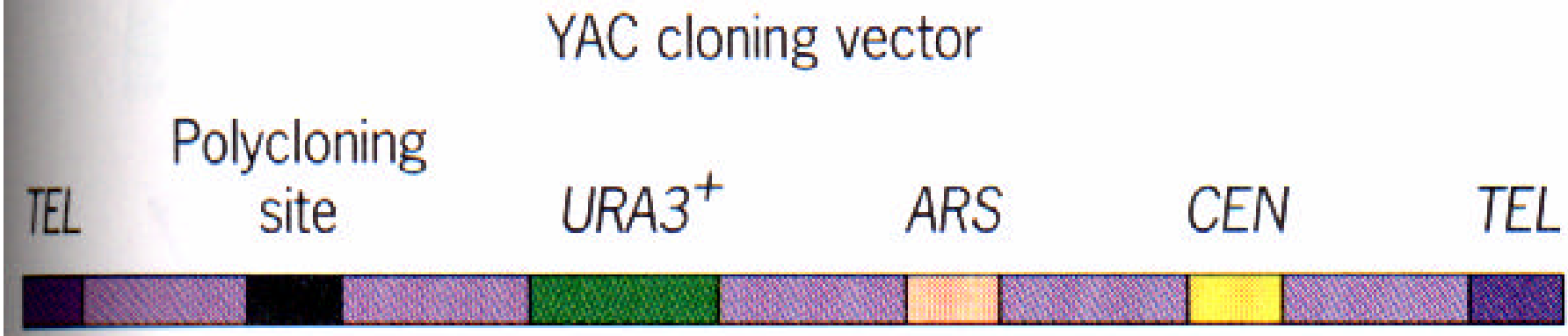
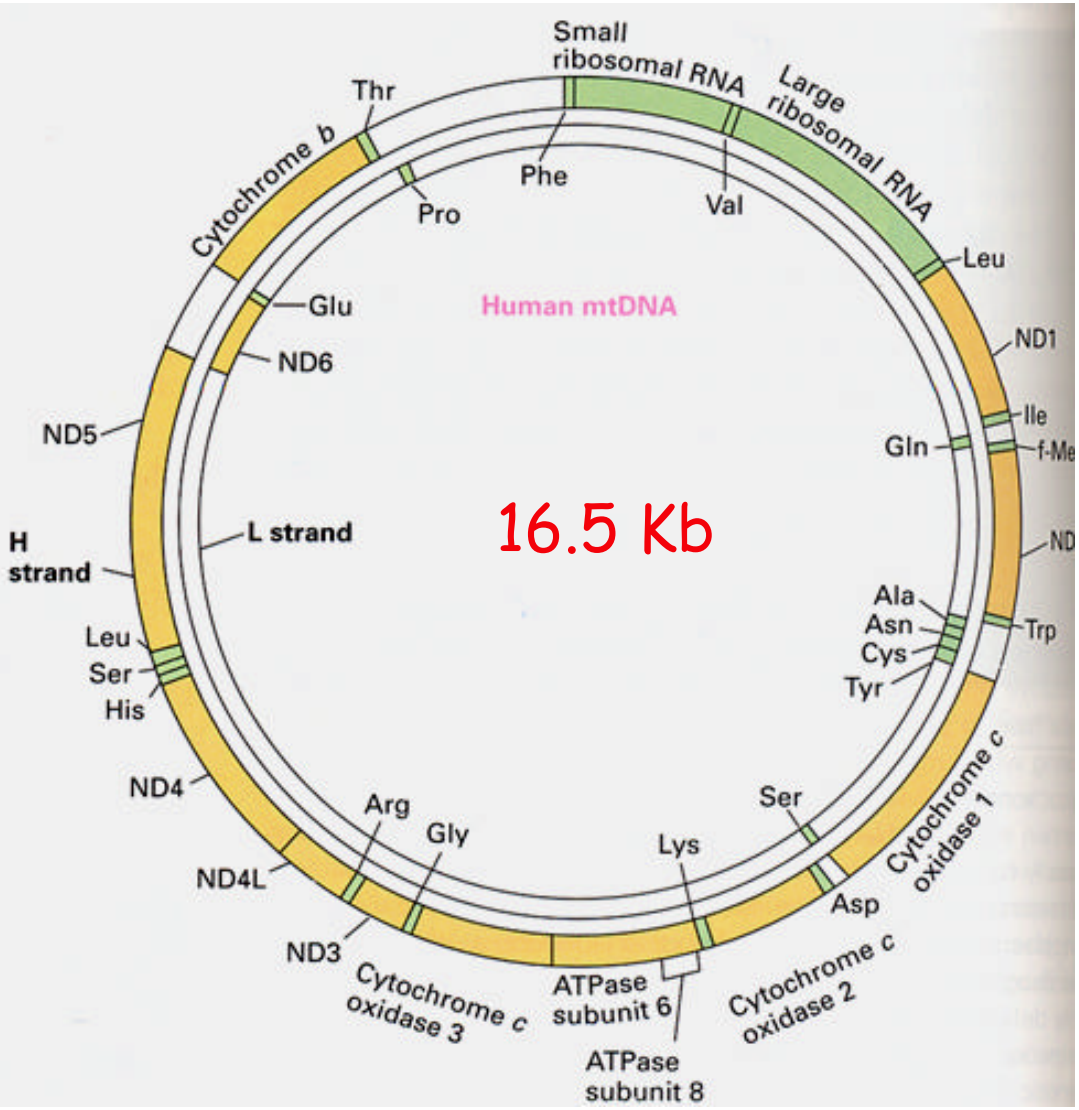


Figure 20.8 Structure of a YAC cloning vector. The components are: (1) *ARS*, autonomously replicating sequence (a yeast origin of replication), (2) *CEN*, a yeast centromere, (3) *TEL*, a yeast telomere, (4) *URA3*$^+$, a wild-type gene required for the biosynthesis of uracil, and (5) the polycloning site, containing the recognition and cleavage sites for a set of restriction endonucleases.

Organelle DNAs

The size and coding capacity of mtDNA vary considerably in different organism



▶ **FIGURE 9-44 Human mitochondrial DNA (mtDNA), which has been sequenced in its entirety.** Proteins and RNAs encoded by each of the two strands are shown separately. Transcription of the outer (H) strand occurs in the clockwise direction and of the inner (L) strand in the counterclockwise direction. The abbreviations for amino acids denote the corresponding tRNA genes. ND1, ND2, etc., denote genes encoding subunits of the NADH-CoQ reductase complex. The 207-bp gene encoding F_0 ATPase subunit 8 overlaps, out of frame, with the N-terminal portion of the segment encoding F_0 ATPase subunit 6. No mammalian mtDNA genes contain introns, although intervening DNA lies between some genes. [See D. A. Clayton, 1991, *Ann. Rev. Cell Biol.* **7**:453.]

Prion -- Sheep, scrapie

New Guinea --Kuru

Mad cow

Prion ---PrP^{c} / PrP^{sc}

Prion

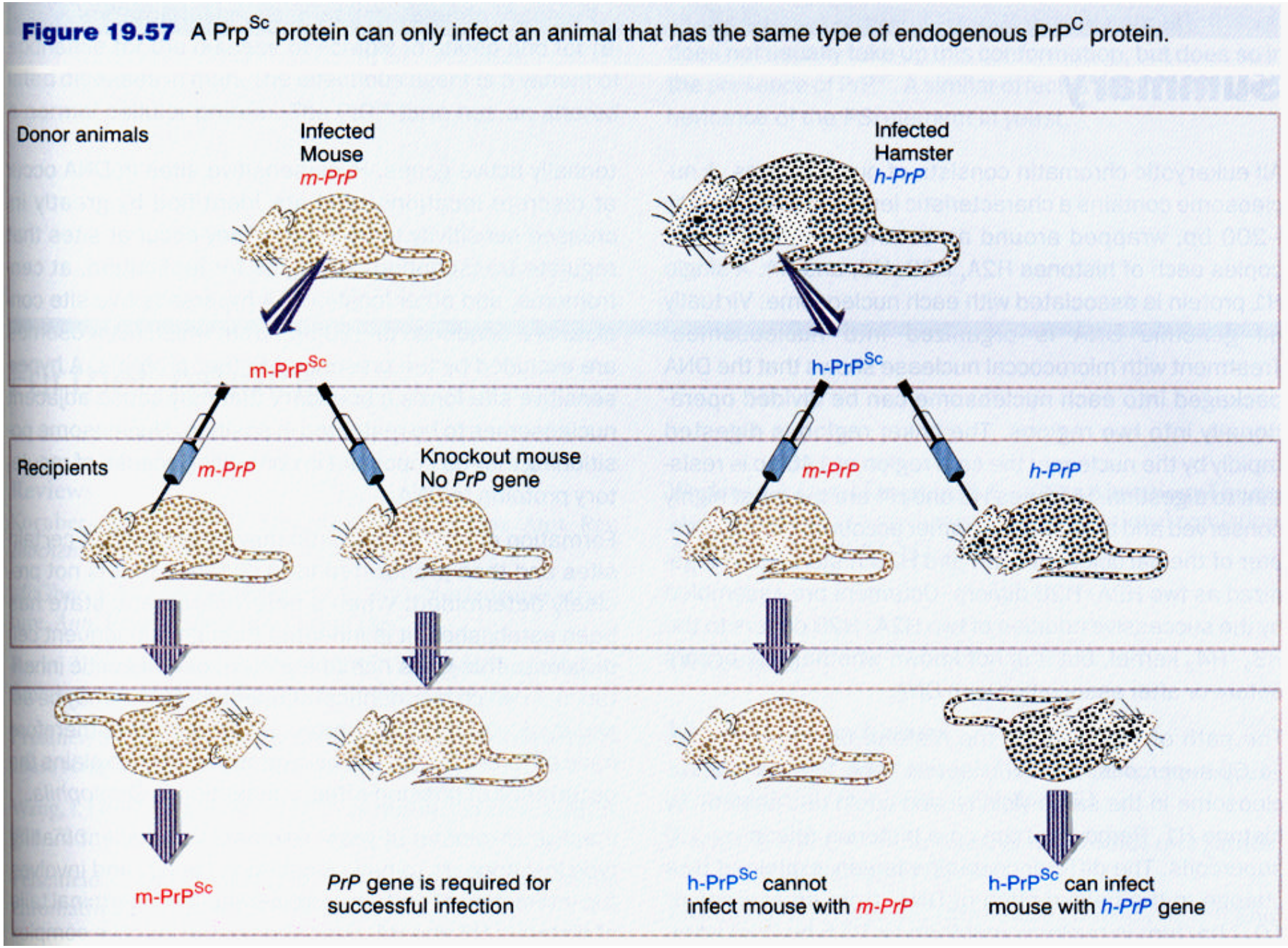
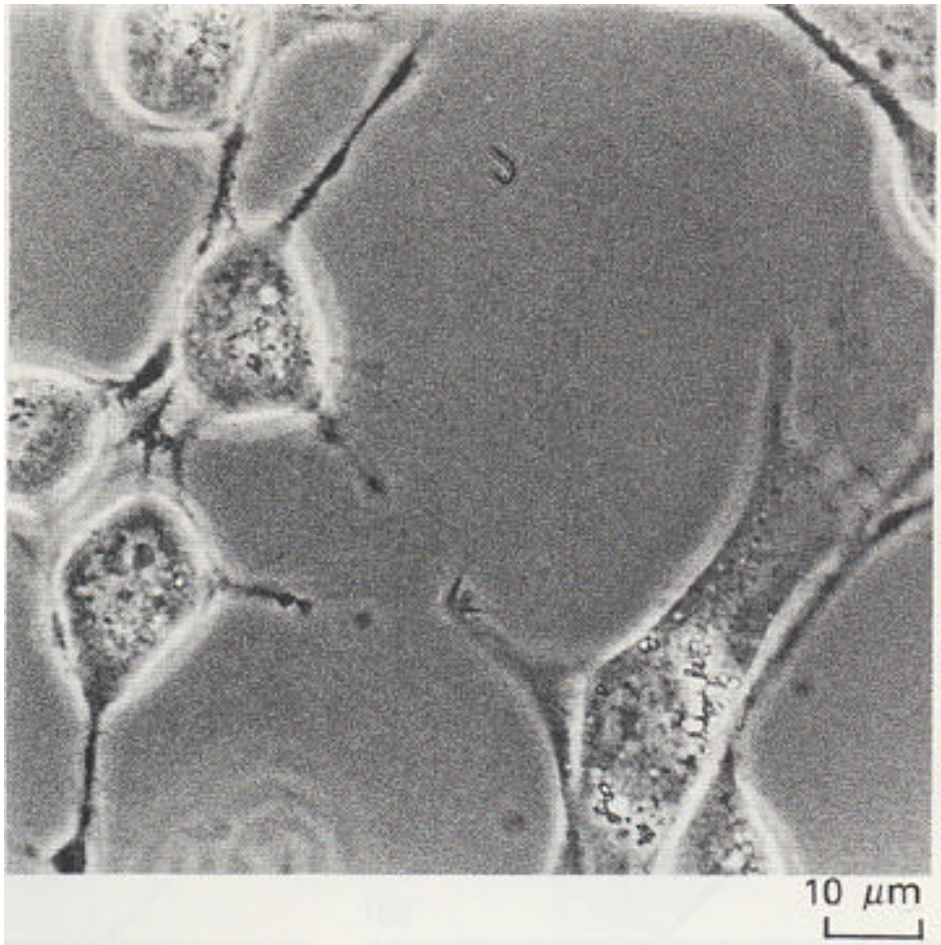
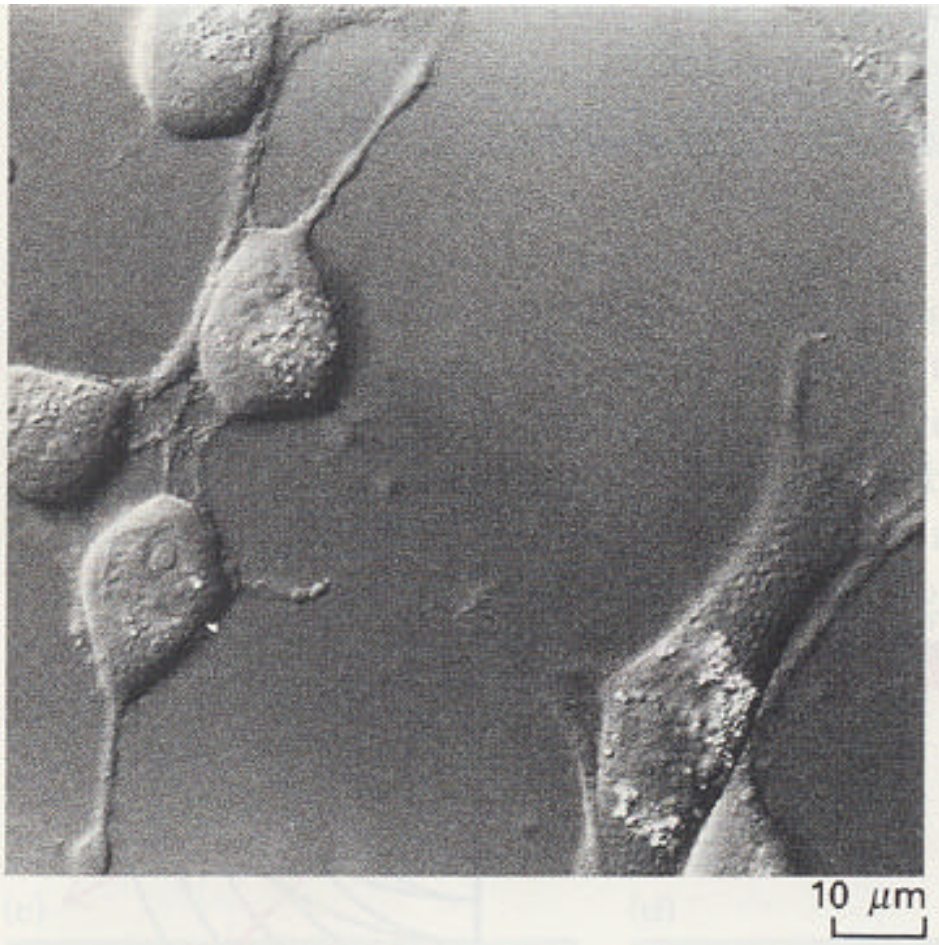


Figure 19.57 A Prp^Sc protein can only infect an animal that has the same type of endogenous PrP^C protein.
Donor animals
Infected Mouse m-PrP
Infected Hamster h-PrP
m-PrP^Sc
h-PrP^Sc
Recipients
m-PrP
Knockout mouse No PrP gene
m-PrP
h-PrP
m-PrP^Sc
PrP gene is required for successful infection
h-PrP^Sc cannot infect mouse with m-PrP
h-PrP^Sc can infect mouse with h-PrP gene


10 μm


10 μm