Chapter 3

Extensions to Mendel's Laws

Sections to study

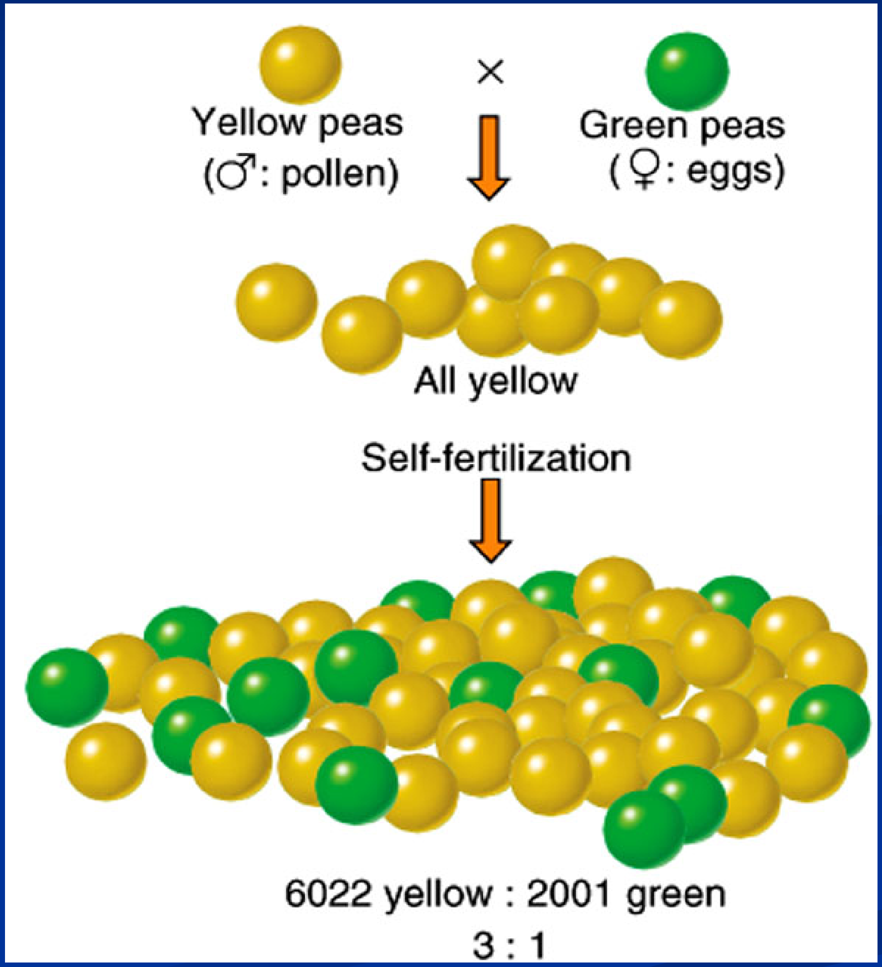
3.1 Extensions to Mendel for single-gene inheritance

- Pairs of alleles show deviations from complete dominance and recessiveness.
- Different forms of the gene are not limited to two alleles.
- One gene may determine more than one trait.

3.2 Extensions to Mendel for multifactorial inheritance

Mendelian pattern of inheritance

- Single-gene trait
- Two alleles
- Clear-cut dominance and recessiveness
- Genotypic ratio 1: 2: 1
- Phenotypic ratio 3: 1



Exceptions to Mendelian pattern of inheritance

- **Single-gene trait**
  - Pairs of alleles show deviations from complete dominance and recessiveness.
  - Different forms of the gene are not limited to two alleles.
  - One gene may determine more than one trait.
- **Multifactorial trait**
  - Traits determined by two or more genes, or by the interaction of genes with the environment.

3.1 Extensions to Mendel for single-gene inheritance

1. Dominance is not always complete

Crosses between true-breeding strains can produce hybrids with phenotypes different from both parents.

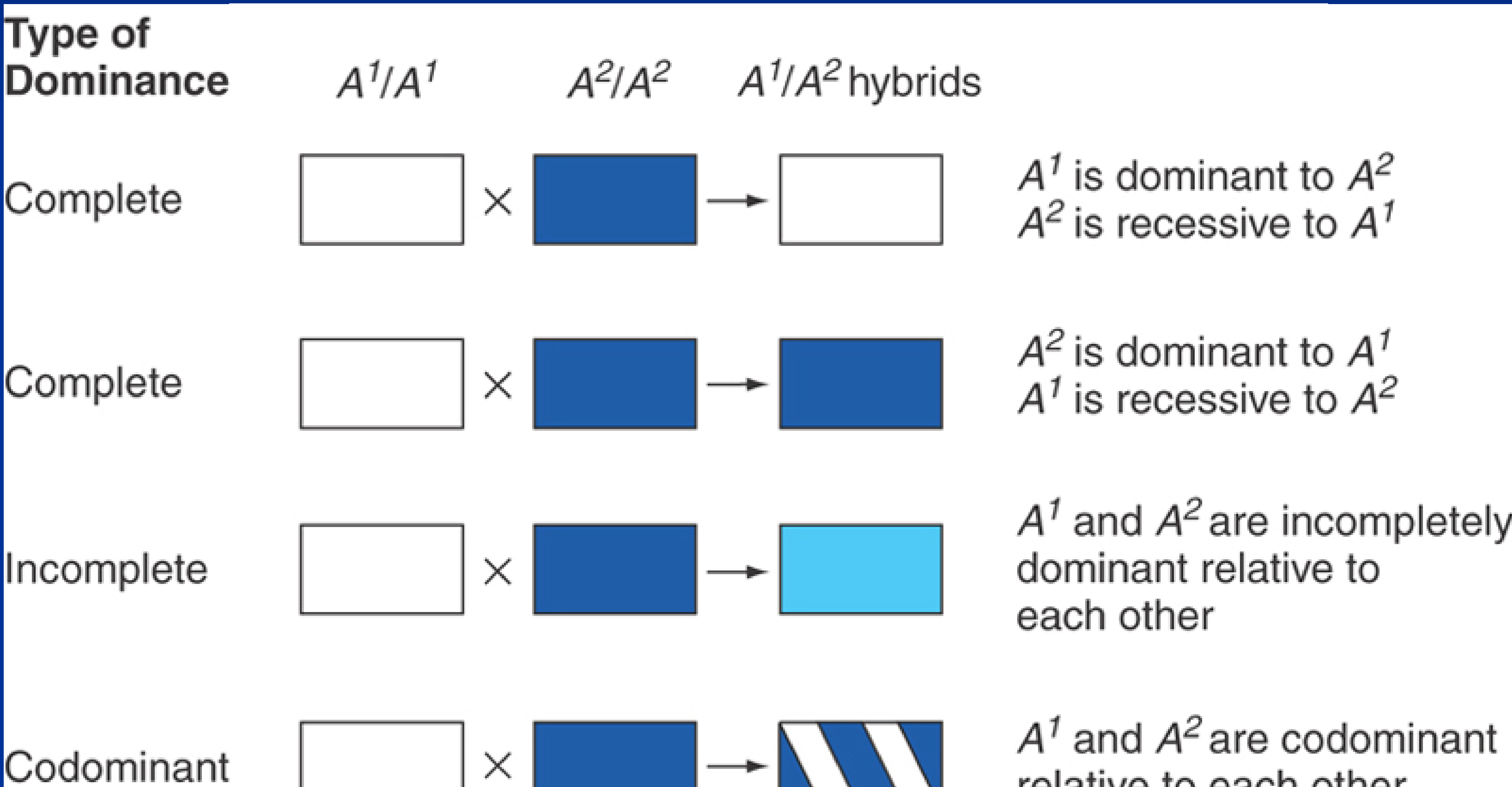


Fig. 3.2

- **Codominance**
  - **F1 hybrids express the traits of both parents.**
  - **Phenotypic ratios are the same as genotypic ratios.**
- **Incomplete dominance**
  - **F1 hybrids express an intermediate phenotype that differs from both parents. Neither allele is dominant or recessive to the other.**
  - **Phenotypic ratios are the same as genotypic ratios.**

Codominant lentil coat patterns

- **Codominance**
  - F1 hybrids express the traits of both parents.
  - Phenotypic ratios are the same as genotypic ratios.

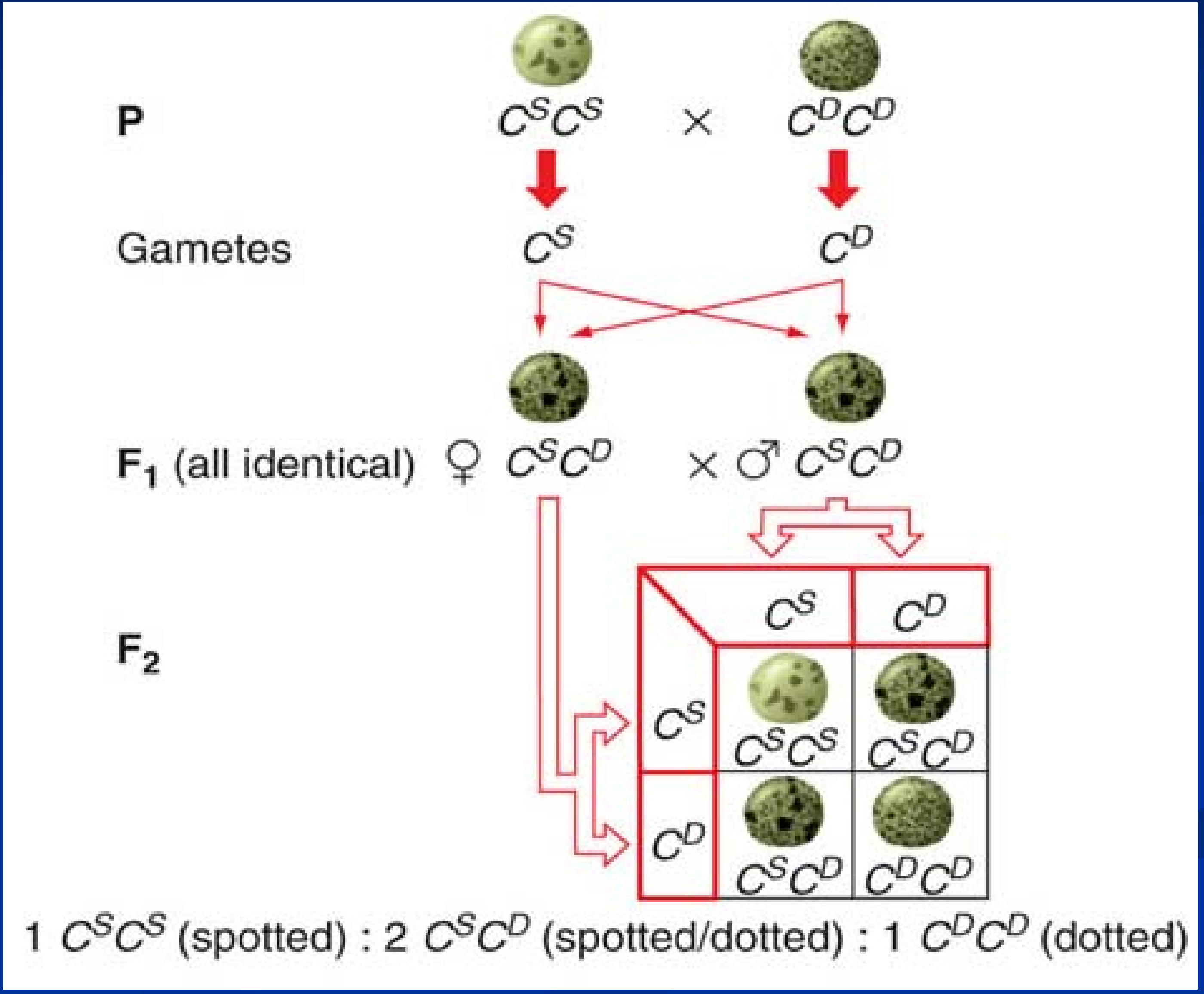


Fig. 3.4a

Codominant blood type alleles

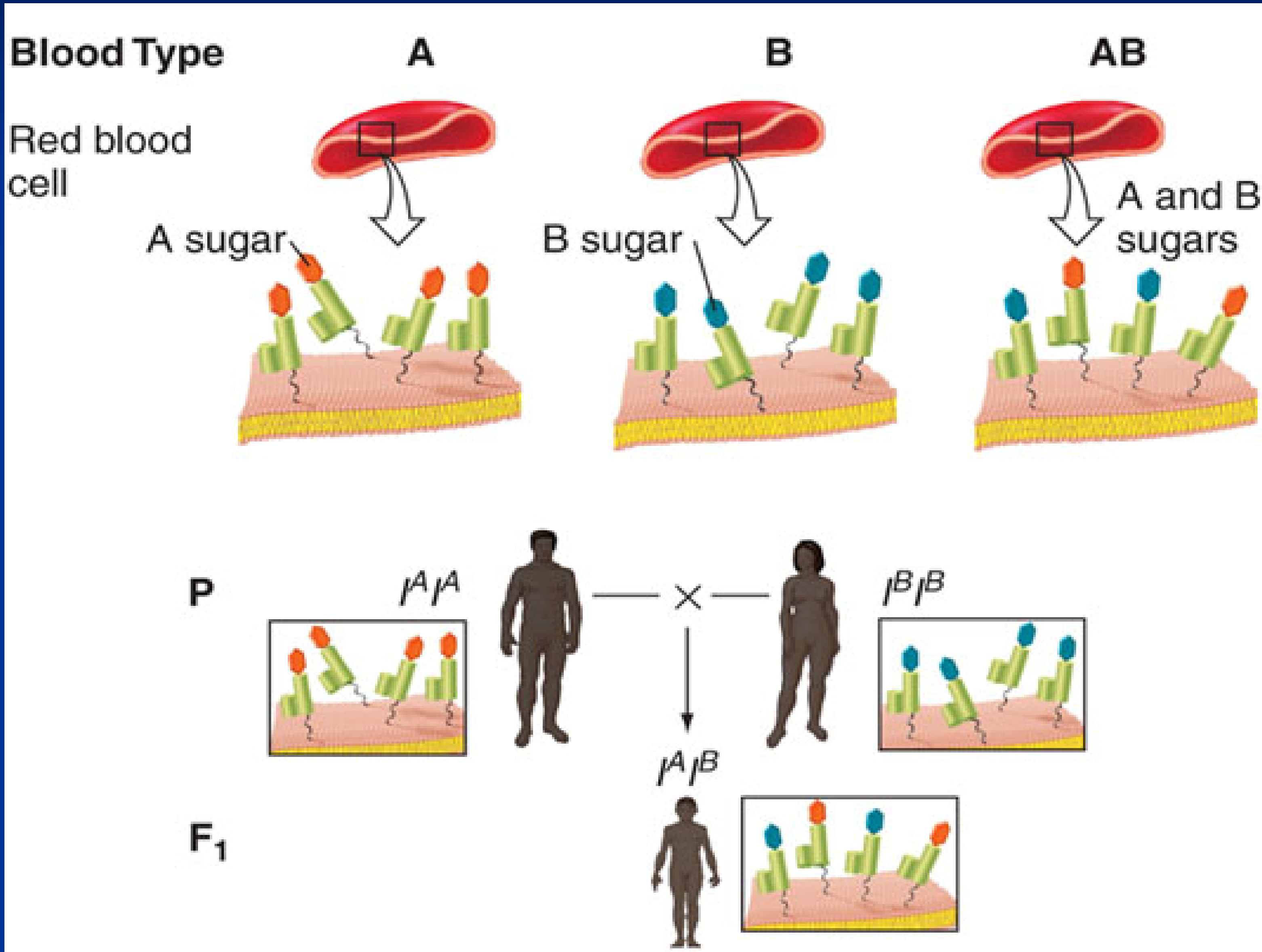
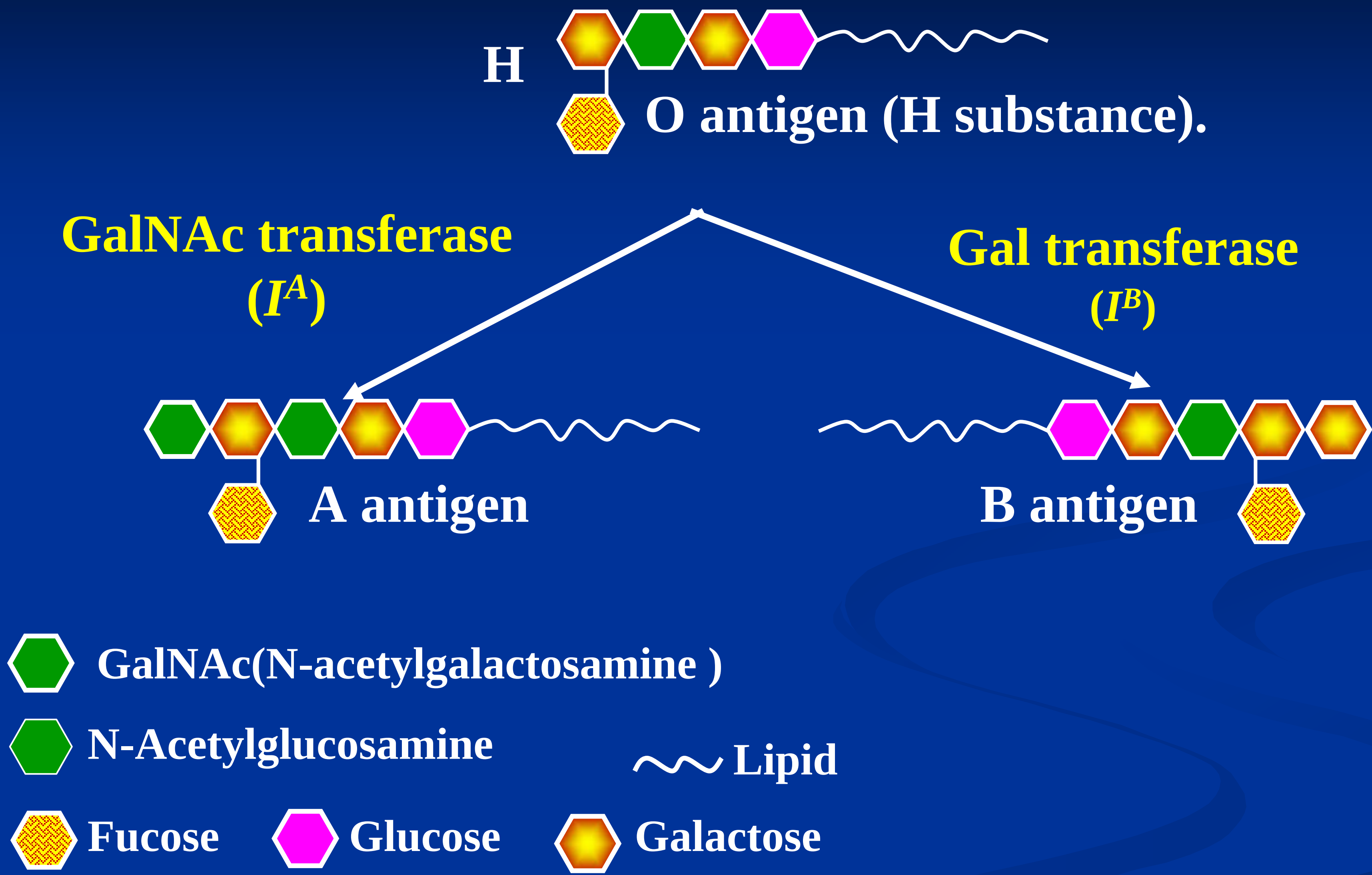


Fig. 3.4b


H
O antigen (H substance).
GalNAc transferase
(I^A)
Gal transferase
(I^B)
A antigen
B antigen
GalNAc(N-acetylgalactosamine)
N-Acetylglucosamine
Lipid
Fucose
Glucose
Galactose

Incomplete dominance in snapdragons

- **Incomplete dominance**
  - F1 hybrids express an intermediate phenotype that differs from both parents. Neither allele is dominant or recessive to the other.
  - Phenotypic ratios are the same as genotypic ratios.

(a) *Antirrhinum majus* (snapdragons)

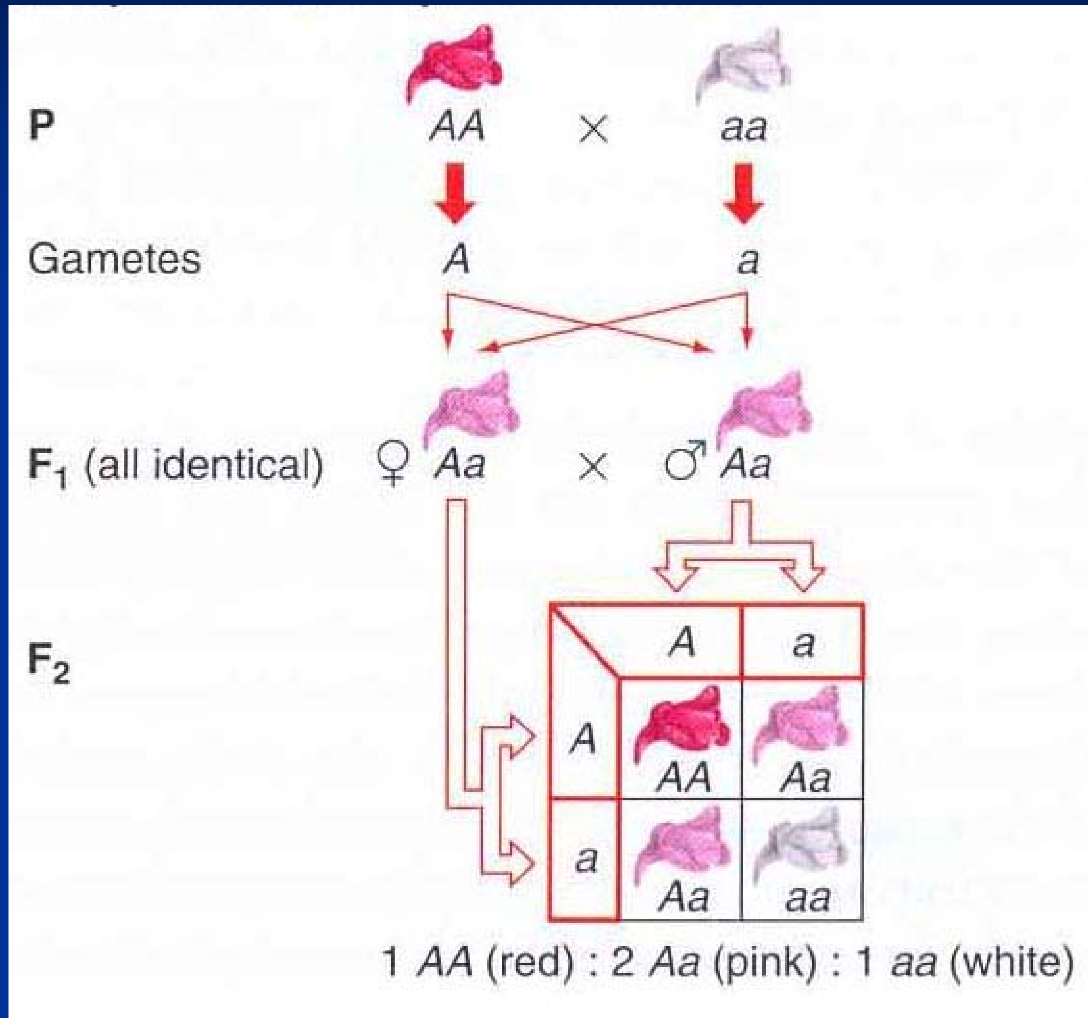


Fig. 3.3

Incomplete dominance arises when phenotype varies in proportion to the amount of functional protein.

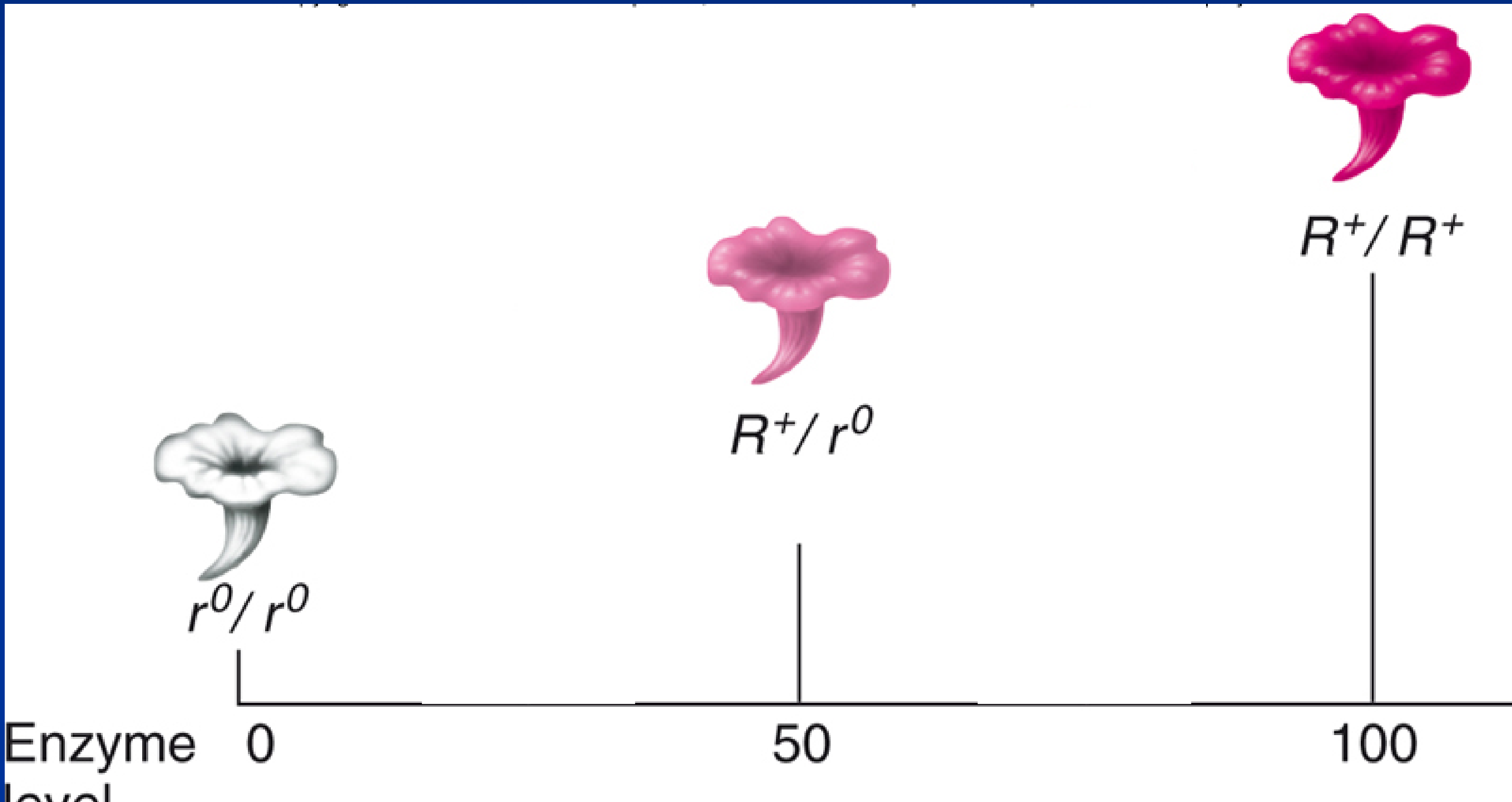


Fig. 8.30

Do variations on dominance relations negate Mendel's law of segregation?

- Mendel's law of segregation still applies.
- Dominance relations do not affect the segregation of alleles.
- Dominance relations only affect phenotype.
  - Gene products control expression of phenotypes differently.

2. A gene may have more than two alleles

- Genes may have multiple alleles in a population.

Human ABO blood types: ***I*** (isoagglutinogen 同族凝集原)

Phenotype	Gene	Genotype	Red blood cell surface antigen	Antibodies in serum
A	I^A	I^AI^A	A	anti-B
		I^Ai		
B	I^B	I^BI^B	B	anti-A
		I^Bi		
AB	I^A, I^B	I^AI^B	A and B	neither
O	i	ii	neither	anti-A and anti-B

- **Each individual carries only two of the alternative alleles.**
  - **ABO blood type**
    - **3 alleles: I^A, I^B, and i**
    - **6 possible ABO genotypes**
- **Dominance or recessiveness is always relative to a second allele.**
  - **ABO blood type**
    - **I^A is completely dominant to i but codominant to I^B**
    - **6 genotypes generate 4 phenotypes**

How to establish dominance relations between multiple alleles?

- Perform reciprocal crosses between pure breeding lines of all phenotypes
- Establish dominance series

Parental Generation: Parental seed coat pattern in cross Parent 1 × Parent 2	F_1 Generation: F_1 phenotype	F_2 Generation: Total F_2 frequencies and phenotypes			Apparent phenotypic ratio
marbled-1 × clear	marbled-1	798	296		3 :1
marbled-2 × clear	marbled-2	123	46		3 :1
spotted × clear	spotted	283	107		3 :1
dotted × clear	dotted	1,706	522		3 :1
marbled-1 × marbled-2	marbled-1	272	72		3 :1
marbled-1 × spotted	marbled-1	499	147		3 :1
marbled-1 × dotted	marbled-1	1,597	549		3 :1
marbled-2 × dotted	marbled-2	182	70		3 :1
spotted × dotted	spotted/dotted	168	339	157	1 : 2 : 1

Dominance series: marbled-1 > marbled-2 > spotted = dotted > clear

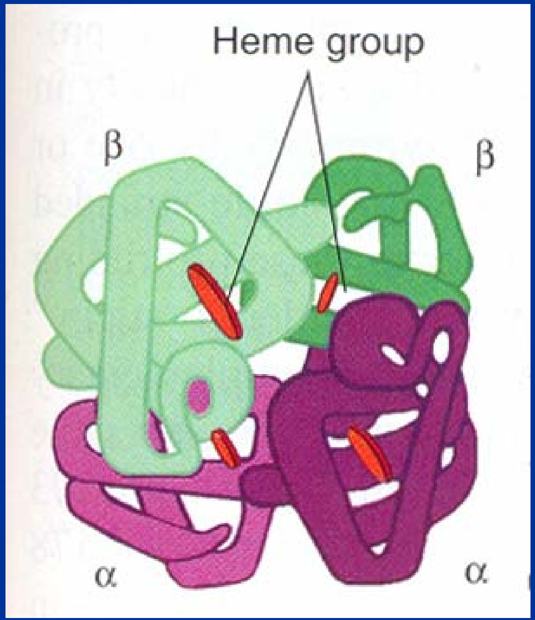
Fig. 3.6

Mutations are the source of new alleles

- **Multiple alleles arise spontaneously in nature due to chance alterations in genetic material – mutations.**

Wild-type —mutation→ **Mutant form**

Example: human β-hemoglobin



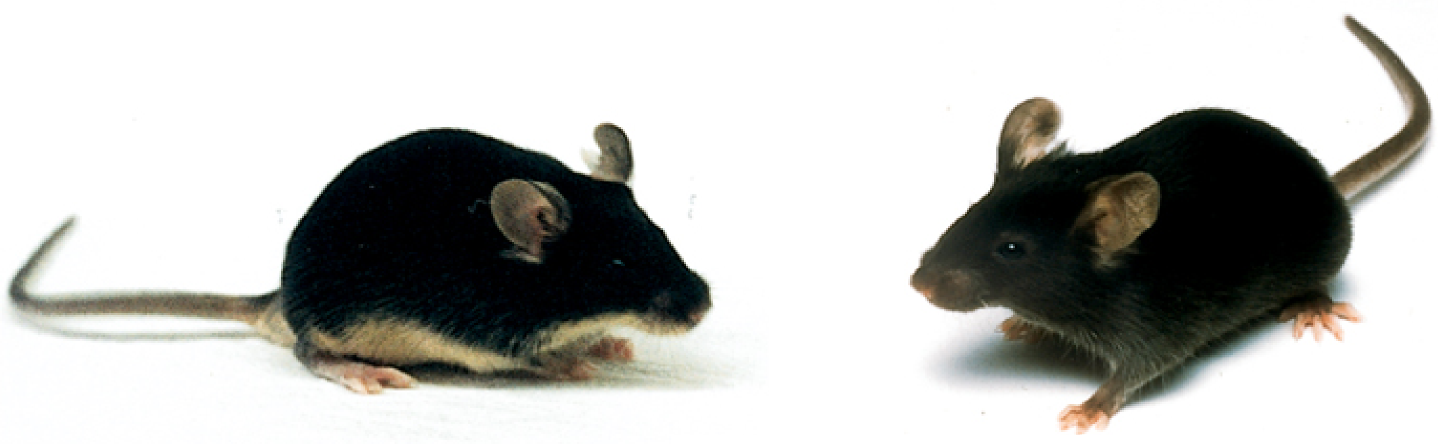
β Chain of Hemoglobin	Sixth code	function
HbA	GAG	normal
HbS	GTG	sickled
HbC	AAG	abnormal

Fig. 9.1a, b

- **Mutation rate varies from 1 in 10,000 to 1 in 1,000,000 per gamete per generation.**
- **Allele frequency is the percentage of the total number of gene copies represented by one allele.**
  - **Wild-type allele – allele whose frequency is more than 1%.**
  - **Mutant allele – allele whose frequency is less than 1%.**
  - **Monomorphic – gene with only one wild-type allele.**
  - **Polymorphic – gene with more than one wild-type allele.**

The mouse *agouti* gene: one wild-type allele, many mutant alleles (> 14)

(a) *Mus musculus* (house mouse) coat colors



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(b) Alleles of the *agouti* gene

Genotype	Phenotype
A–	agouti
$a^t a^t$	black/yellow
aa	black
$a^t a$	black/yellow

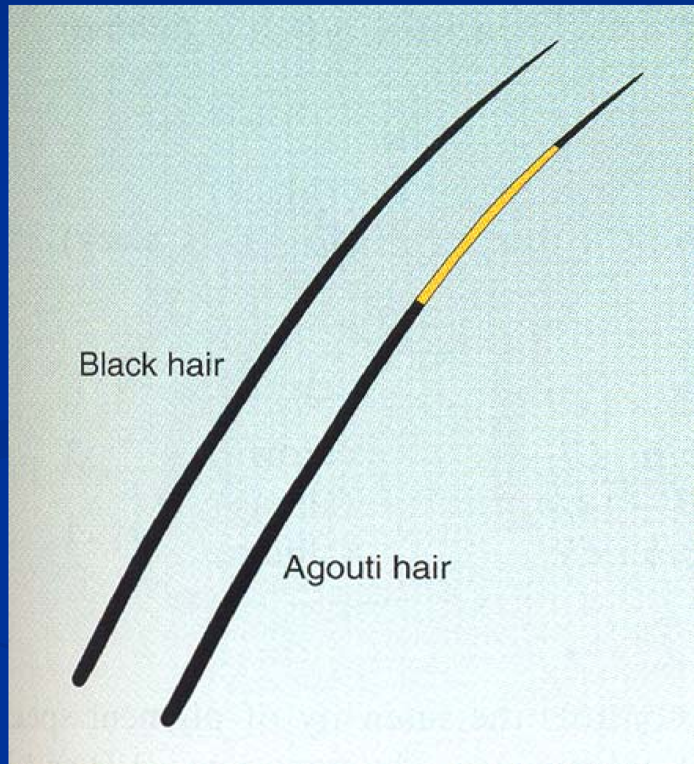


Fig. 3.7a-b

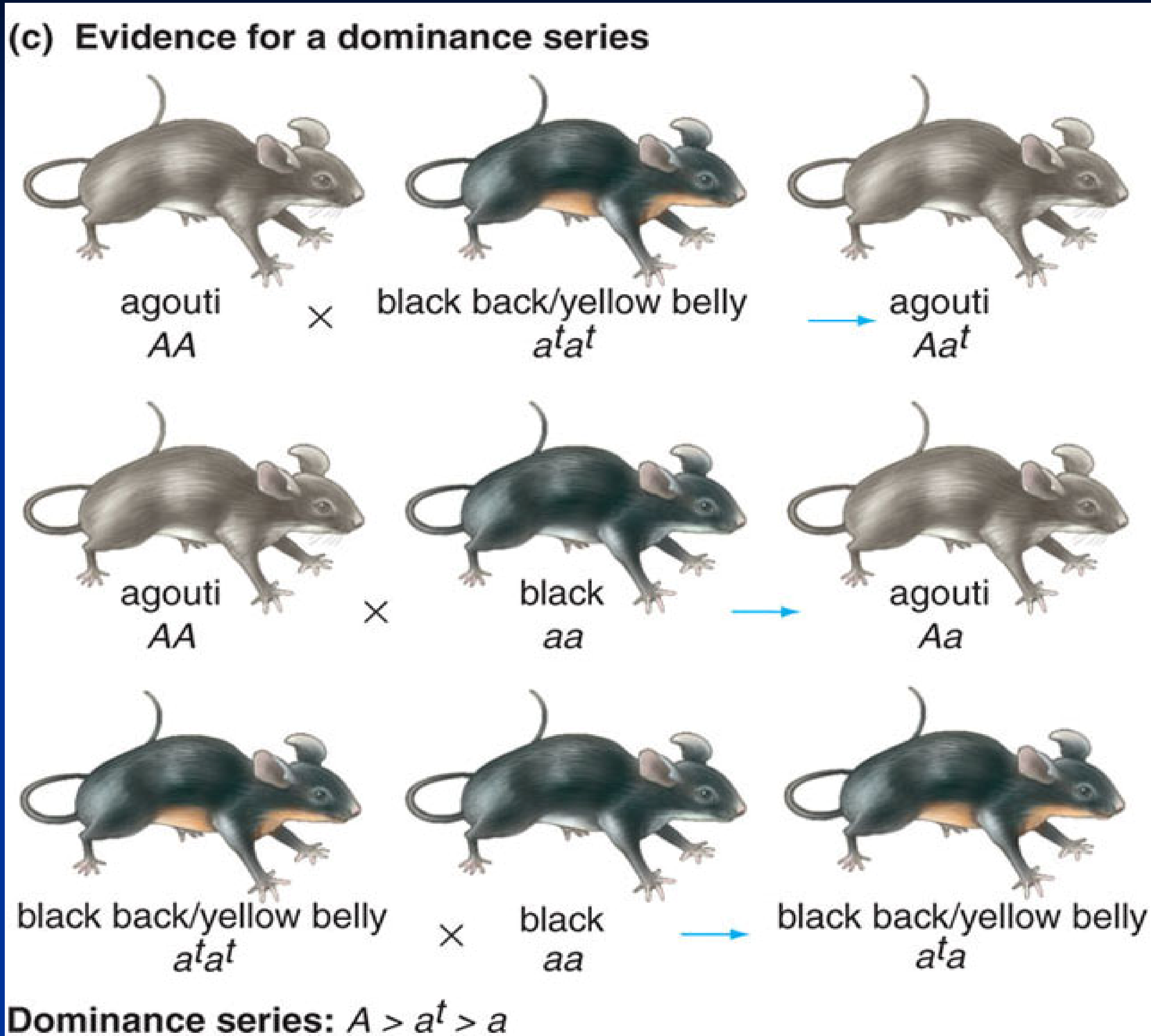
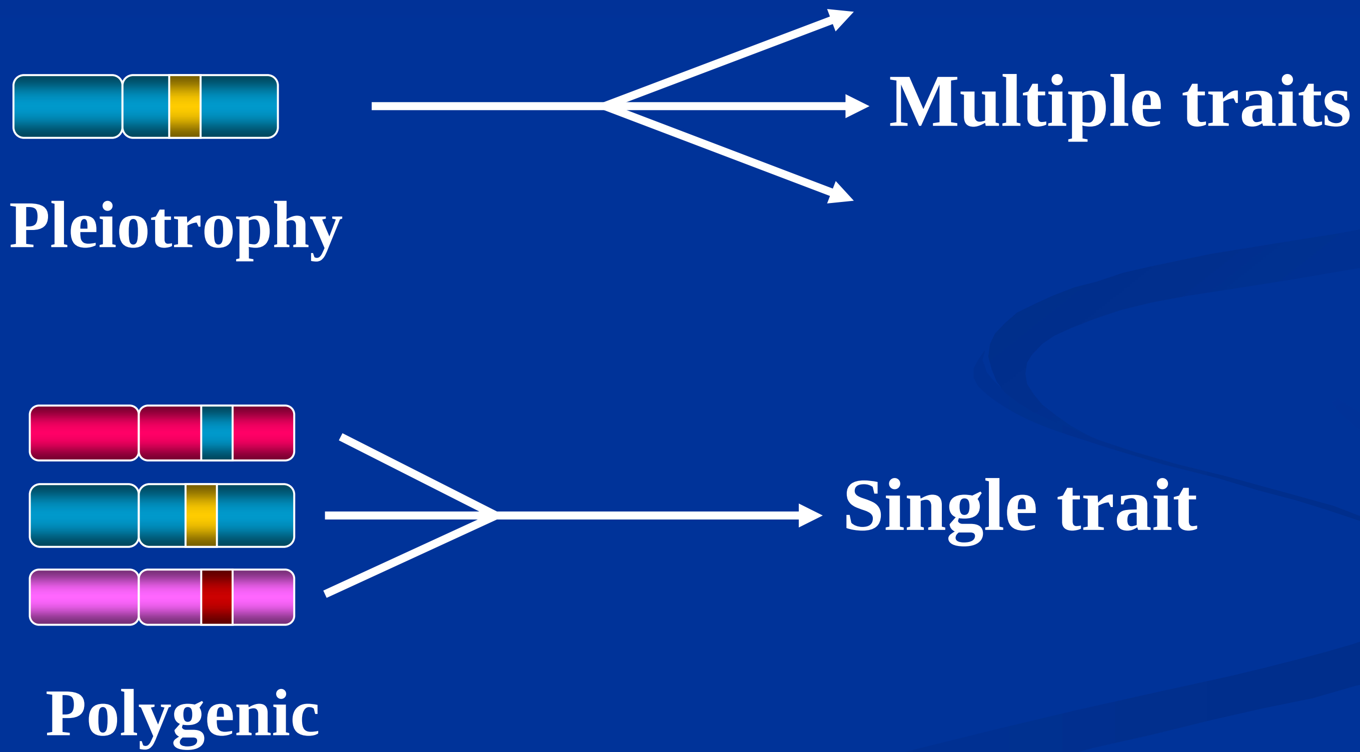

(c) Evidence for a dominance series
agouti
AA
×
black back/yellow belly
a^ta^t
agouti
Aa^t
agouti
AA
×
black
aa
agouti
Aa
black back/yellow belly
a^ta^t
×
black
aa
black back/yellow belly
a^ta
Dominance series: $A > a^t > a$

Fig. 3.7c

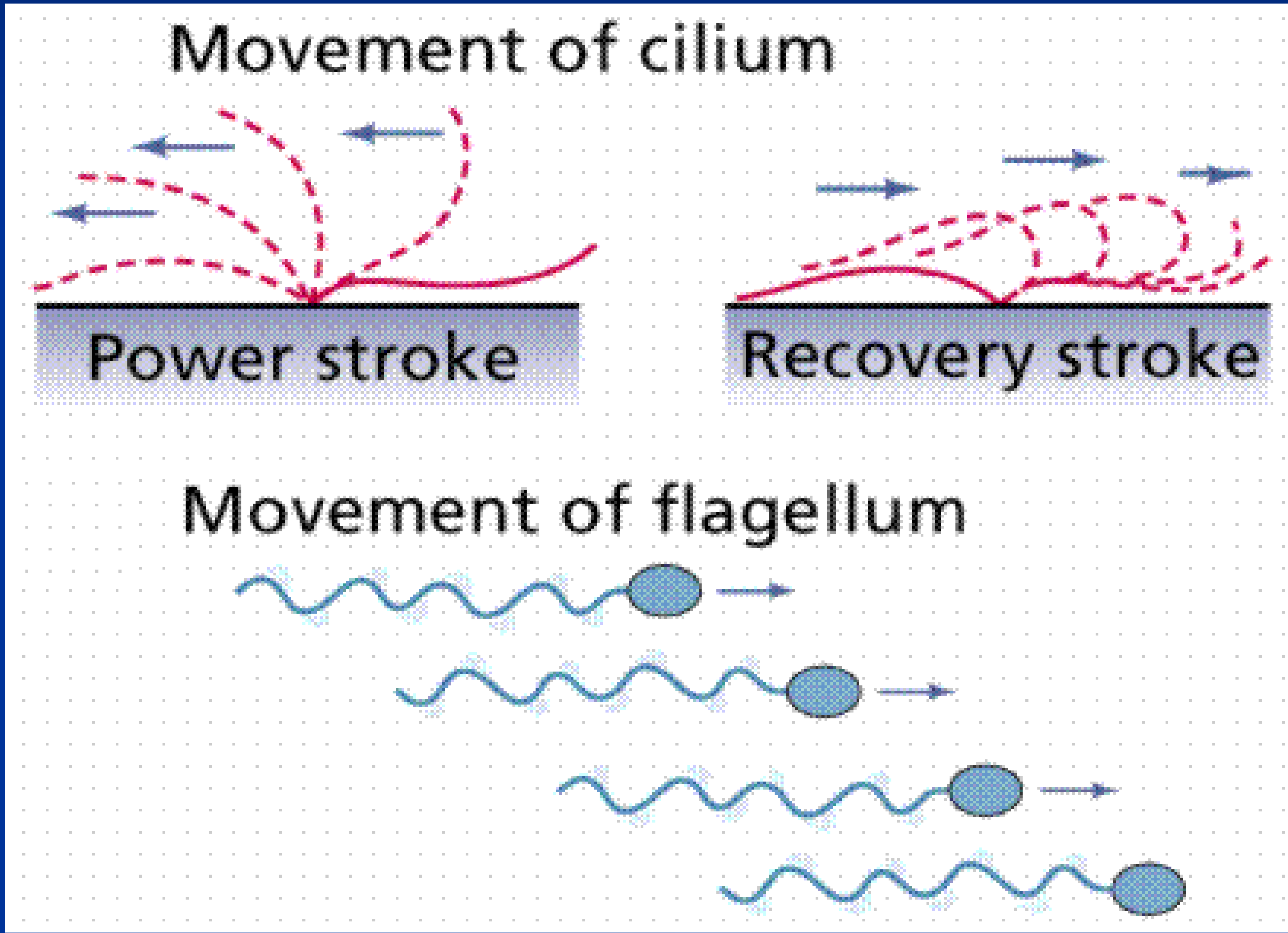
3. One gene may contribute to several visible characteristics

- **Pleiotropy – A single gene determines a number of distinct and seemingly unrelated characteristics.**



- **Pleiotropy** – A single gene determines a number of distinct and seemingly unrelated characteristics.
  - One recessive mutation in Maori people causes respiratory problems and infertility in men.

- **Defects in cilia of respiratory system and flagella in sperm are the cause for the Maori disease.**



- **Some alleles affect viability.**
  - **Alleles that affect viability often produce deviations from a 1:2:1 genotypic and 3:1 phenotypic ratio.**

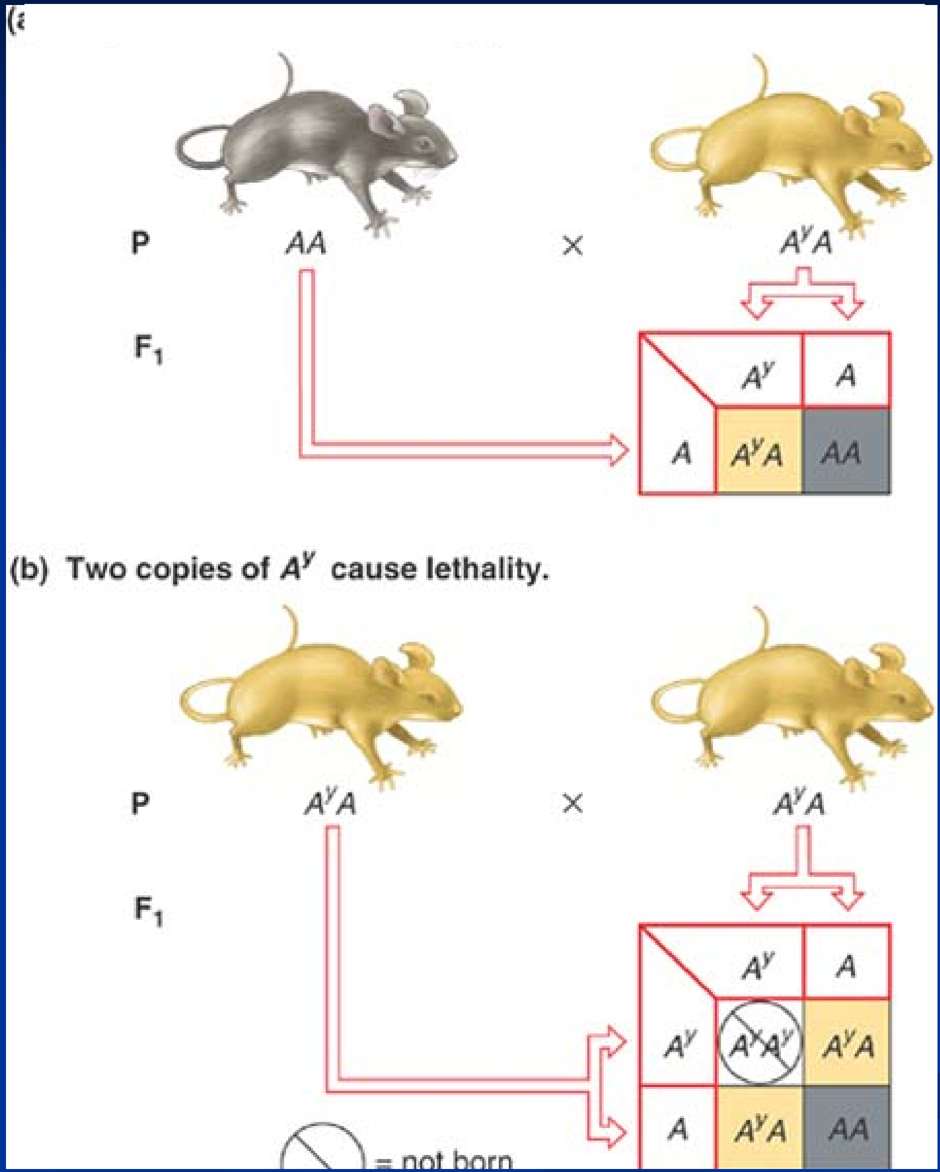


Fig. 3.9

A dominant coat color allele also produces recessive lethality in mice

- A^Y is dominant to A in determining coat color.
  - Yellow must be A^YA.
- A^Y is recessive to A in producing viability.
  - Yellow mice do not breed true.
  - A^YA^Y die *in utero* and do not show up as progeny.

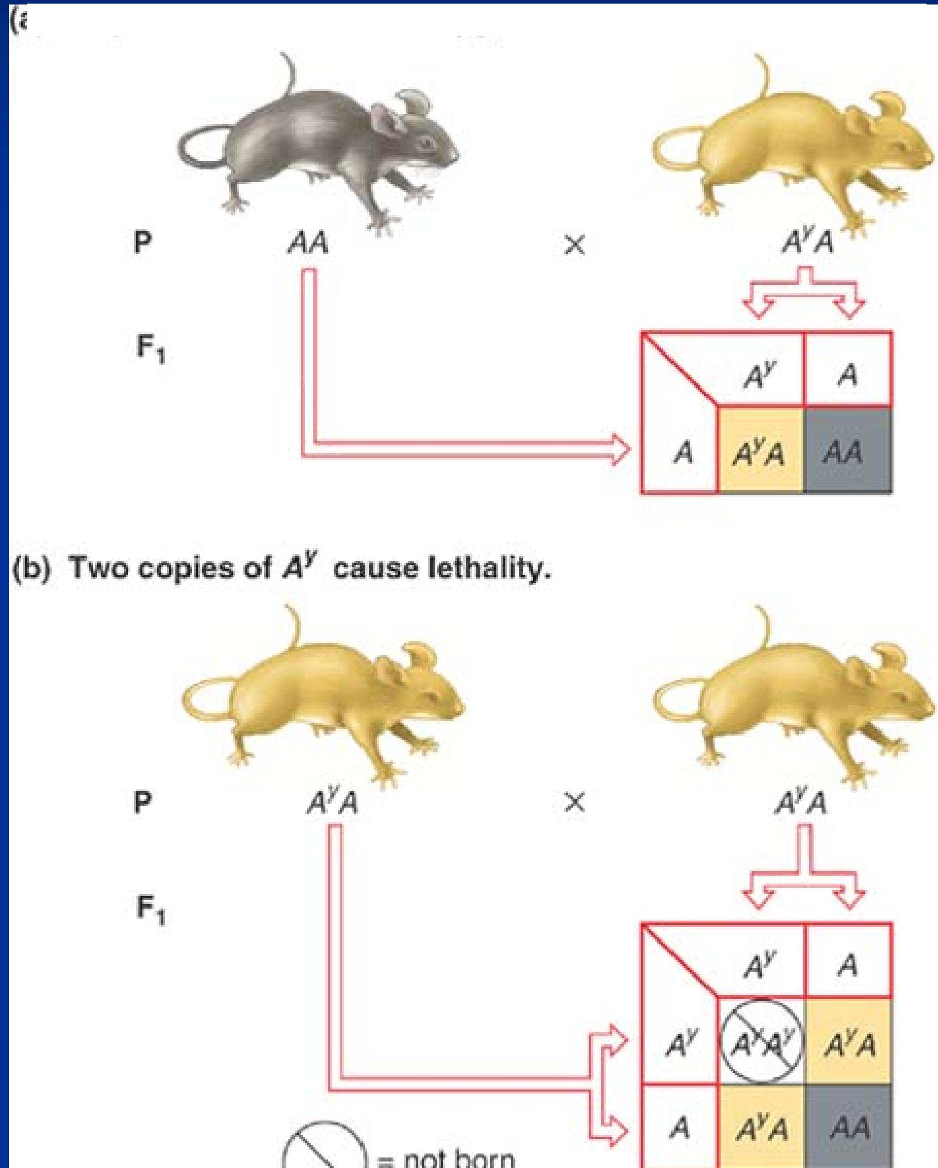


Fig. 3.9

TABLE 3.1 For Traits Determined by One Gene: Extensions to Mendel's Analysis Explain Alterations of the 3:1 Monohybrid Ratio

What Mendel Described	Extension	Extension's Effect on Heterozygous Phenotype	Extension's Effect on Ratios Resulting from an $F_1 \times F_1$ Cross
Complete dominance	Incomplete dominance Codominance	Unlike either homozygote	Phenotypes coincide with genotypes in a ratio of 1:2:1
Two alleles	Multiple alleles	Multiplicity of phenotypes	A series of 3:1 ratios
All alleles are equally viable	Recessive lethal alleles	No effect	2:1 instead of 3:1
One gene determines one trait	Pleiotropy: one gene influences several traits	Several traits affected in different ways, depending on dominance relations	Different ratios, depending on dominance relations for each affected trait

Sickle-cell anemia

Mutant β chain (E6V) of hemoglobin forms aggregates that cause red blood cells to sickle.

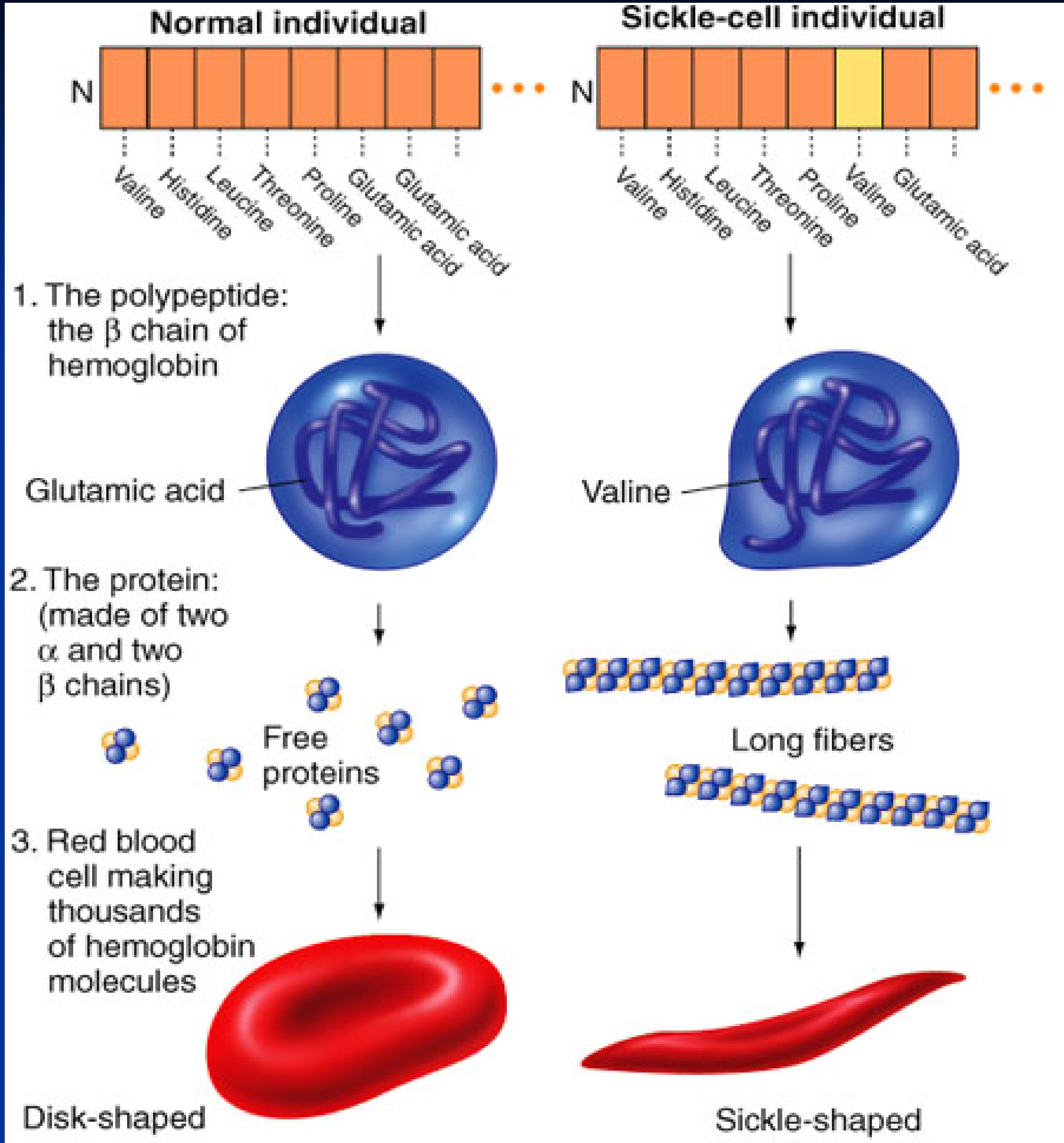
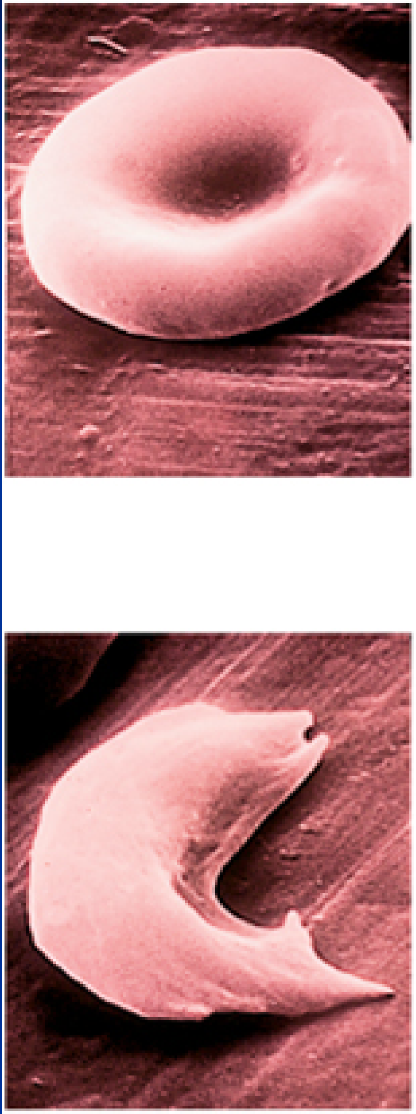


Fig. 7.25a

- **Multiple alleles**
  - **Wild-type is $Hb\beta^{A}$**
  - **More than 400 mutant alleles identified so far**
  - **$Hb\beta^{S}$ allele specifies abnormal peptide causing sickling among red blood cells**
- **Pleiotropy**
  - **$Hb\beta^{S}$ affects more than one trait**
    - **Muscle cramps, shortness of breath, and fatigue**
    - **Anemia**
    - **Resistance to malaria**
- **Recessive lethality**
  - **Homozygous $Hb\beta^{S}\ Hb\beta^{S}$ individuals die at young age.**
- **Different dominance relations**
  - **Heterozygous $Hb\beta^{A}\ Hb\beta^{S}$ individuals become sick in low-oxygen environment.**

Pleiotropy of sickle-cell anemia



(a)

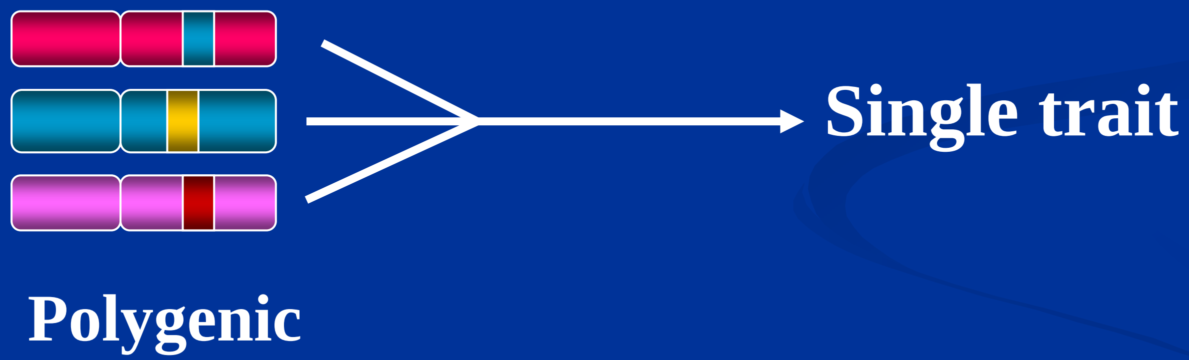
Phenotypes at Different Levels of Analysis	Normal $Hb\beta^A Hb\beta^A$	Carrier $Hb\beta^A Hb\beta^S$	Diseased $Hb\beta^S Hb\beta^S$	Dominance Relations at Each Level of Analysis
β-globin polypeptide production				$Hb\beta^A$ and $Hb\beta^S$ are codominant
Red blood cell shape at sea level	Normal	Normal	Sickled cells present	$Hb\beta^A$ is dominant $Hb\beta^S$ is recessive
Red blood cell concentration at sea level	Normal	Normal	Lower	
Red blood cell shape at high altitudes	Normal	Sickled cells present	Severe sickling	$Hb\beta^A$ and $Hb\beta^S$ show incomplete dominance
Red blood cell concentration at high altitudes	Normal	Lower	Very low, anemia	
Susceptibility to malaria	Normal susceptibility	Resistant	Resistant	$Hb\beta^S$ is dominant $Hb\beta^A$ is recessive

(b)

Fig. 3.10

3.2 Extensions to Mendel for multifactorial inheritance

- **Novel phenotypes can emerge from the combined action of the alleles of two genes.**



P *AABB* × *aabb*

F1 ♀ *AaBb* × ♂ *AaBb*

F2

	AB	*Ab*	*aB*	*ab*
AB	*AABB*	*AABb*	*AaBB*	*AaBb*
Ab	*AABb*	*AAbb*	*AaBb*	*Aabb*
aB	*AbBB*	*AaBb*	*aaBB*	*aaBb*
ab	*AaBb*	*Aabb*	*aaBb*	*aabb*

9 *A_ B_*

3 *A_ bb*

3 *aa B_*

1 *aa bb*

1. Two genes interact to produce new phenotypes

- **Genes A and B interact to produce new colors in lentils.**

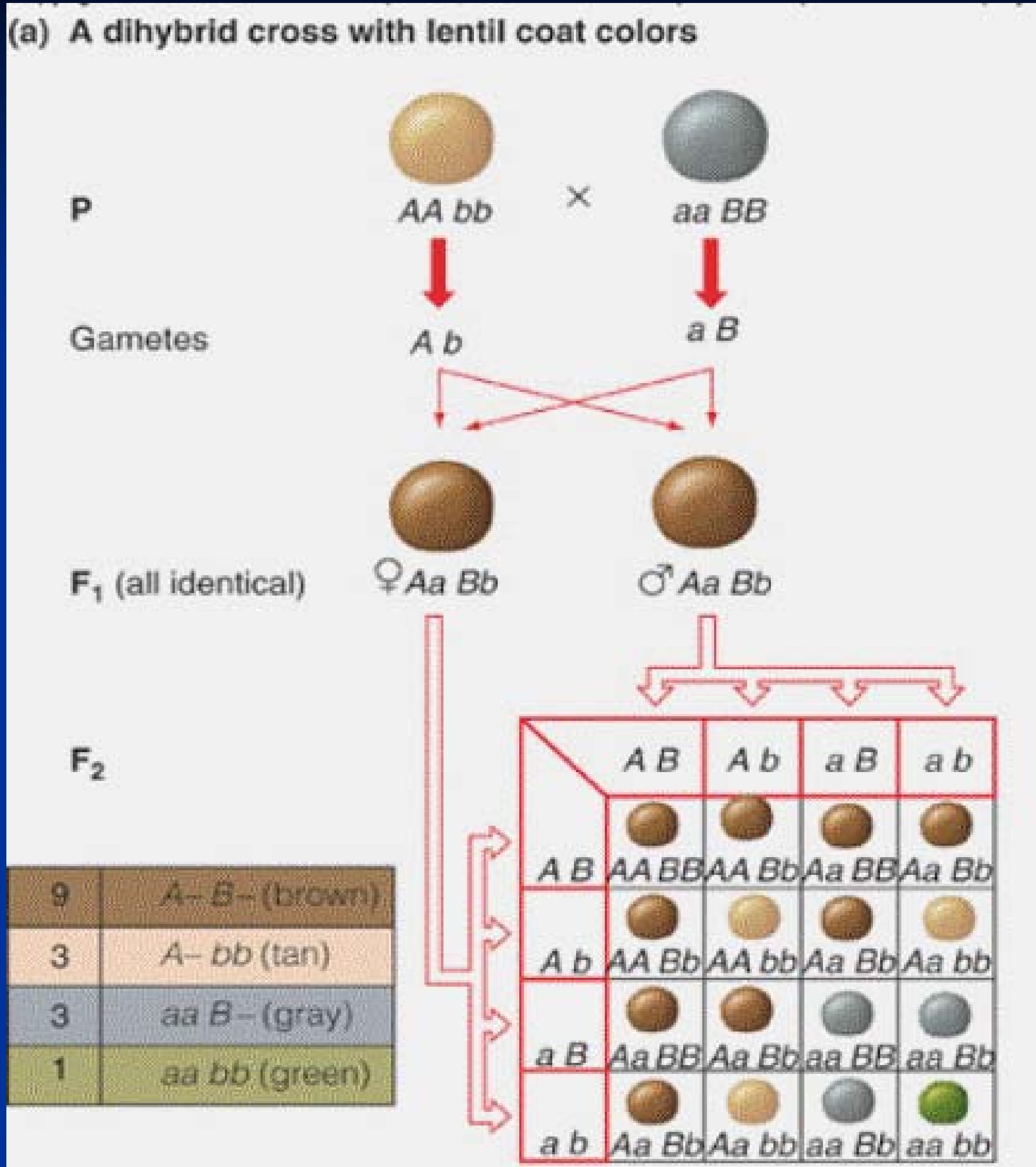
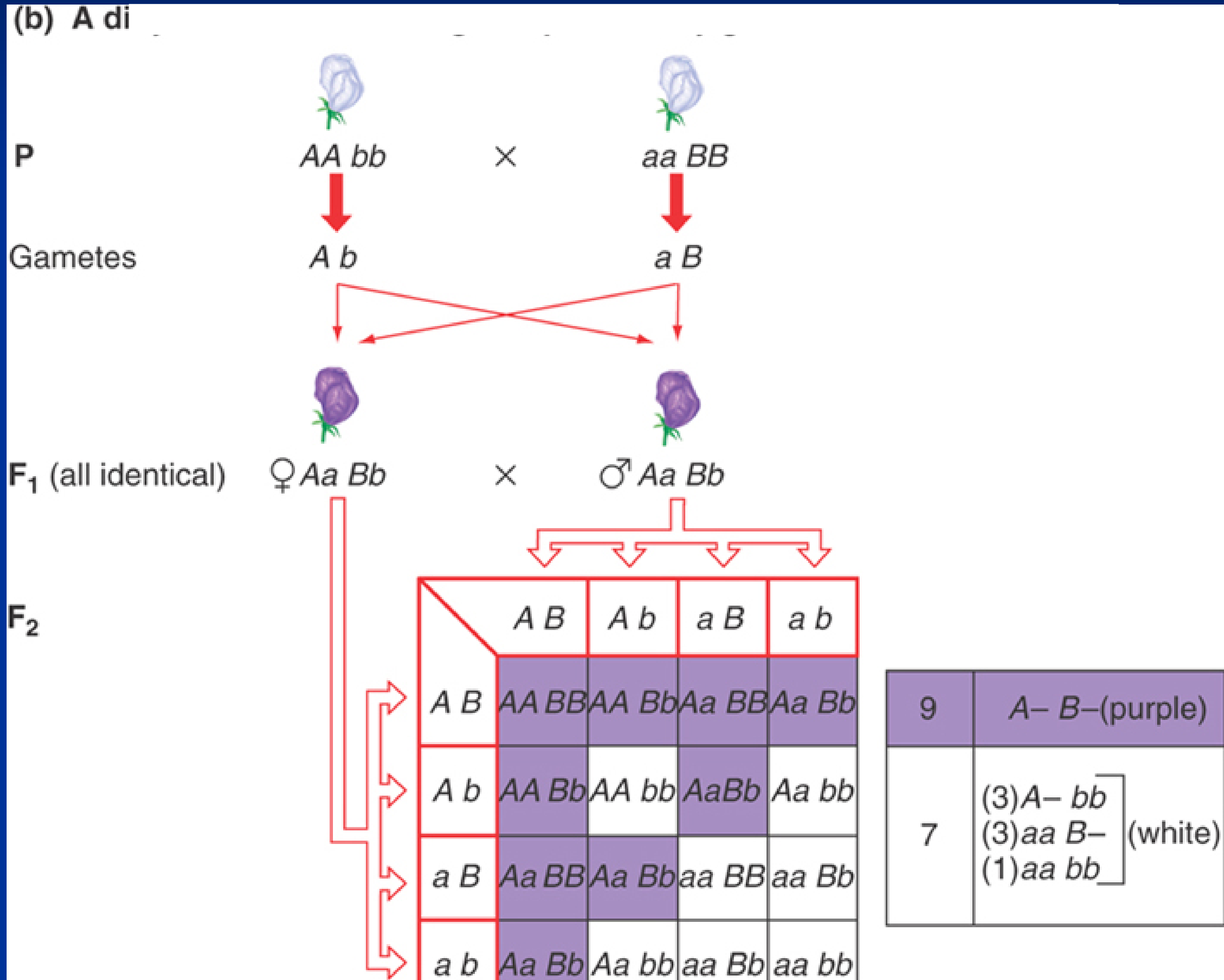


Fig. 3.11a

2. Complementary gene action generates flower color in sweet peas

(a) *Lathyrus odoratus* (sweet peas)



9:7 (purple: white) ratio demonstrates that one dominant allele of two genes must be present to produce purple flowers.

Fig. 3.12

Two genes work in tandem to produce purple pigment

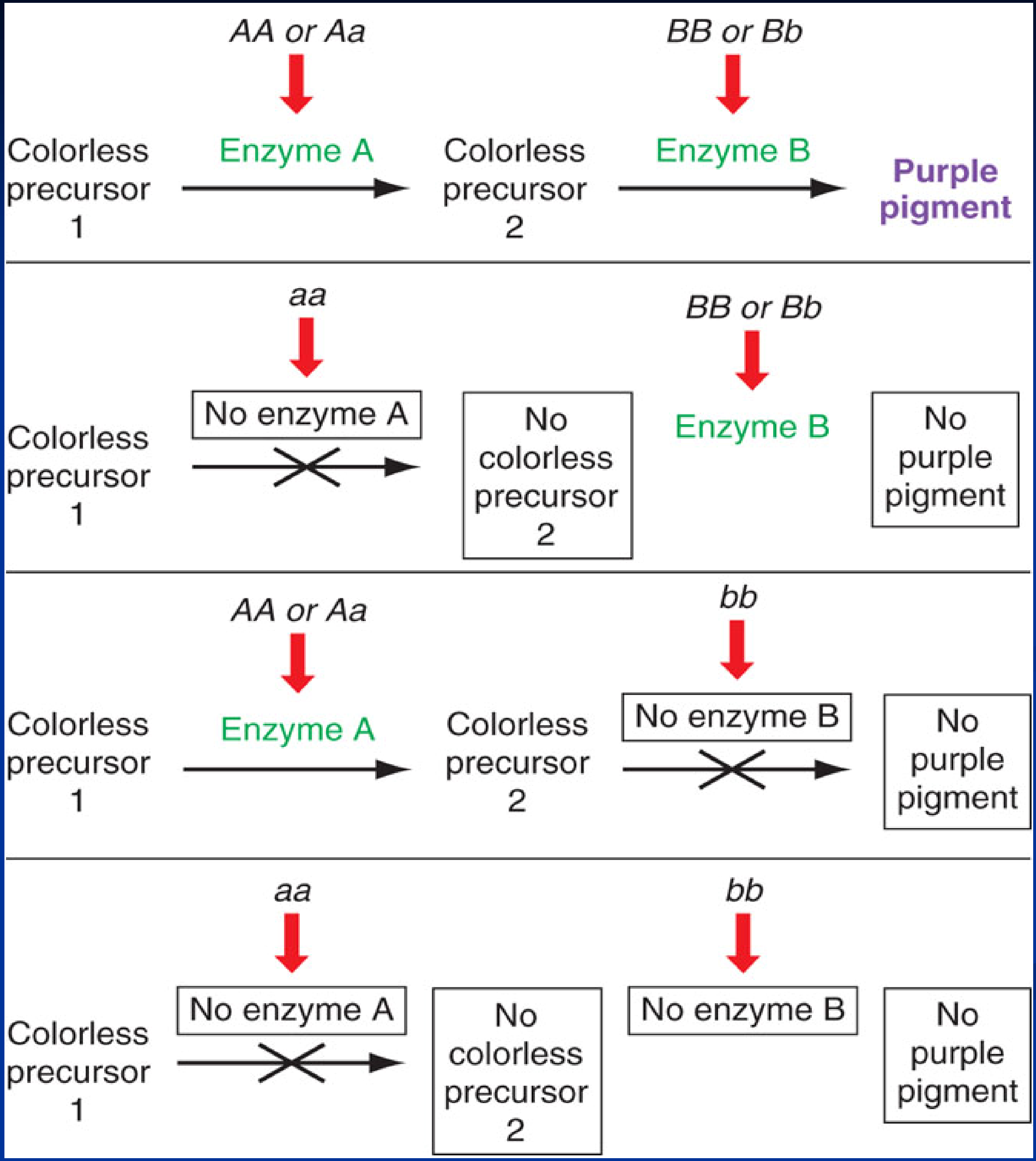
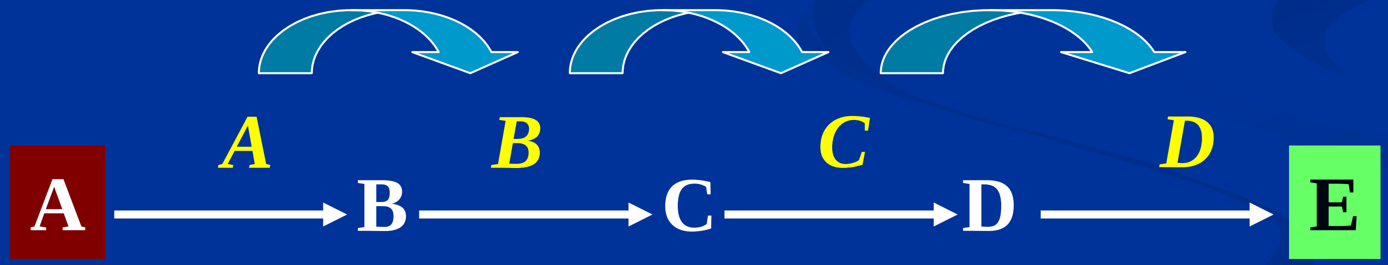


Fig. 3.13

3. One gene's alleles mask the effects of another gene's alleles

- **Epistasis: A gene interaction in which the effects of an allele at one gene hide the effects of alleles at another gene.**
  - **Recessive epistasis – The recessive allele of one gene hides the effects of another gene.**
  - **Dominant epistasis – The dominant allele of one gene hides the effects of another gene.**



***A*: epistatic gene**
***B*: hypostatic gene**

3-1 Recessive epistasis
Coat color in Labrador retrievers

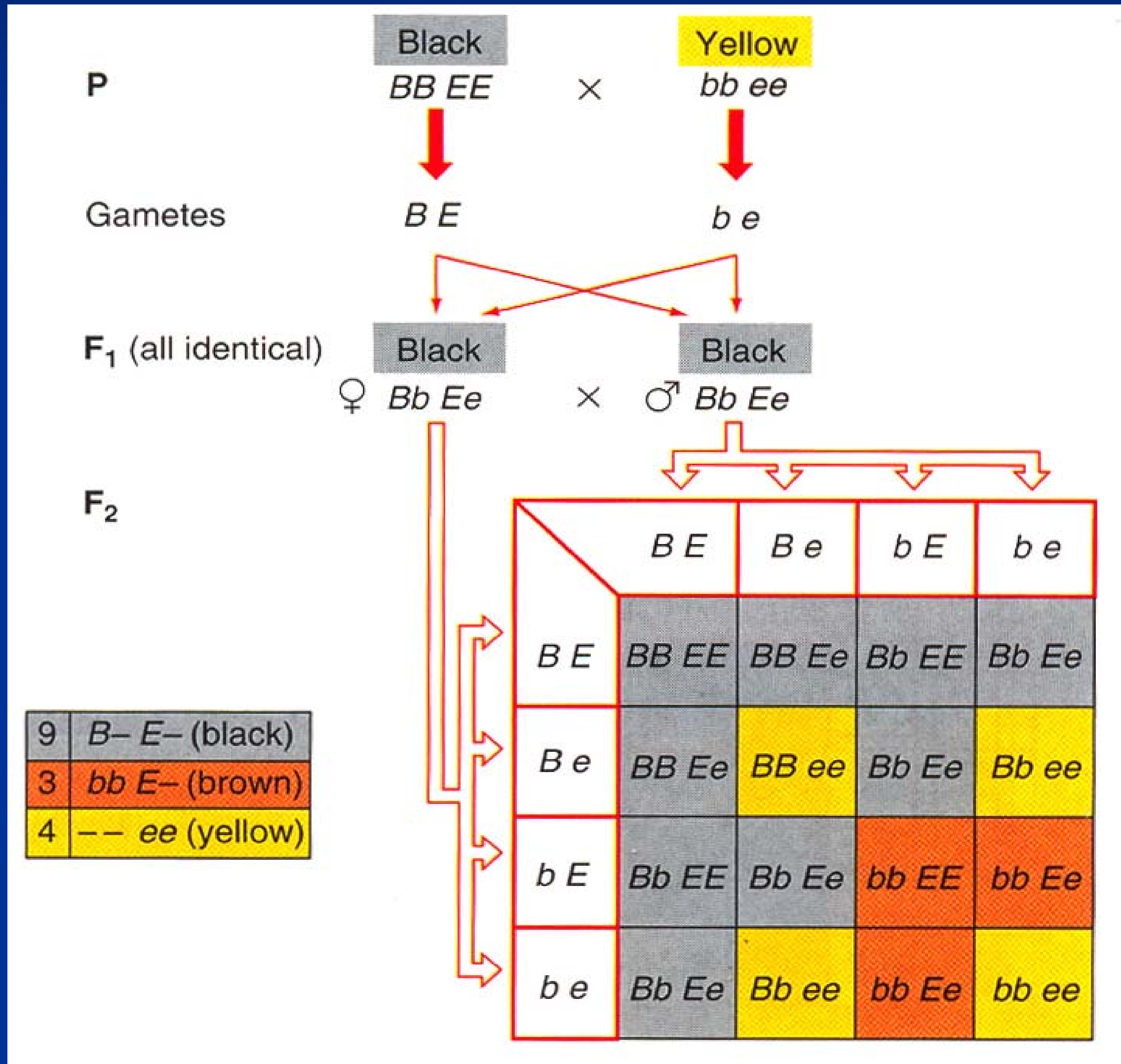
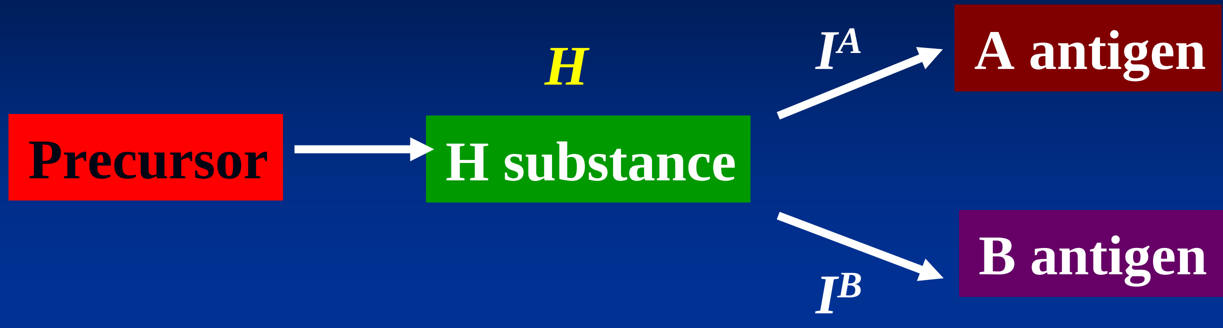


Fig. 3.14a

Recessive epistasis in human blood types

Bombay phenotype – mutant recessive allele at second gene *hh* masks phenotype of ABO alleles.



Woman (O type) I^AI^B *hh* — **Man** (O type) *ii Hh*

Children

(A, B or O type)

I^Ai *Hh*

I^Bi *Hh*

I^Ai *hh*, I^Bi *hh*

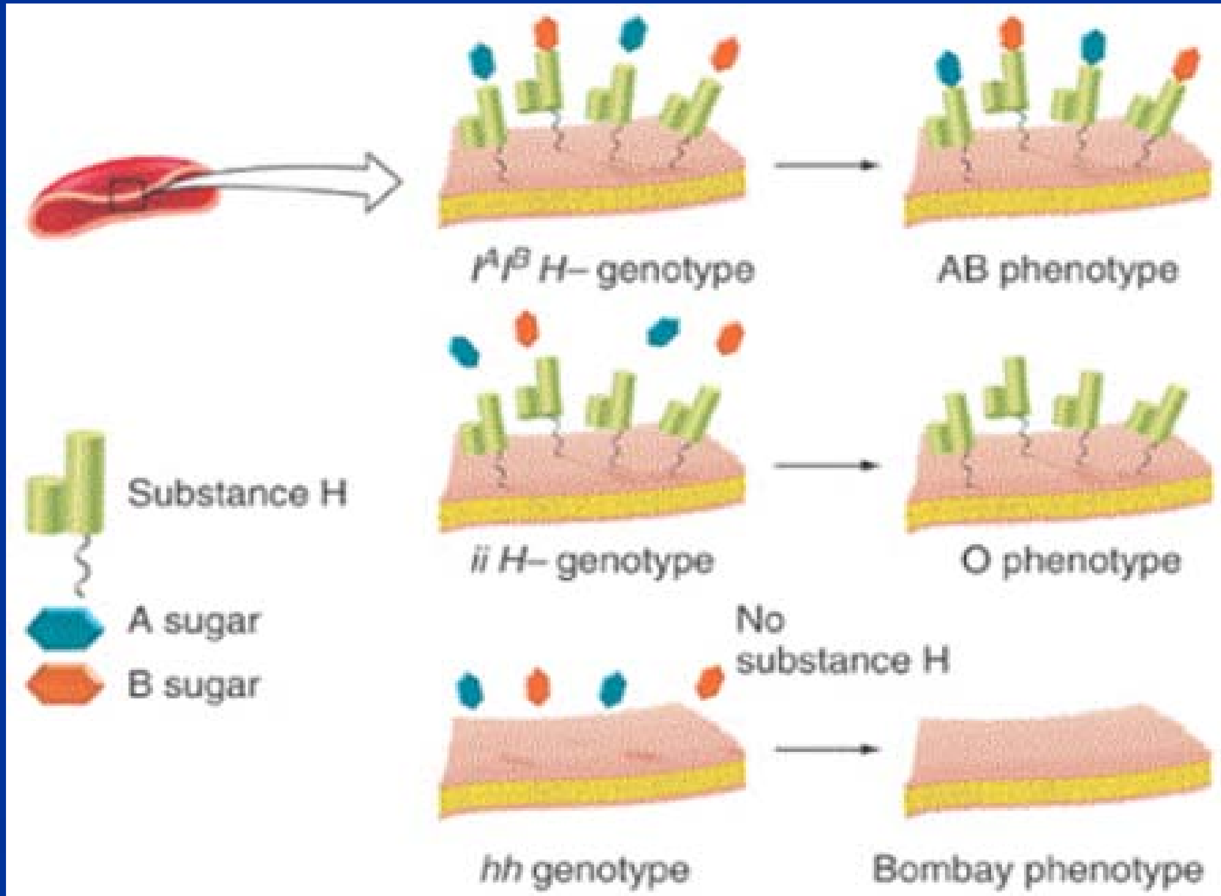


Fig. 3.14b

3-2 Dominant epistasis (I)

Summer squash

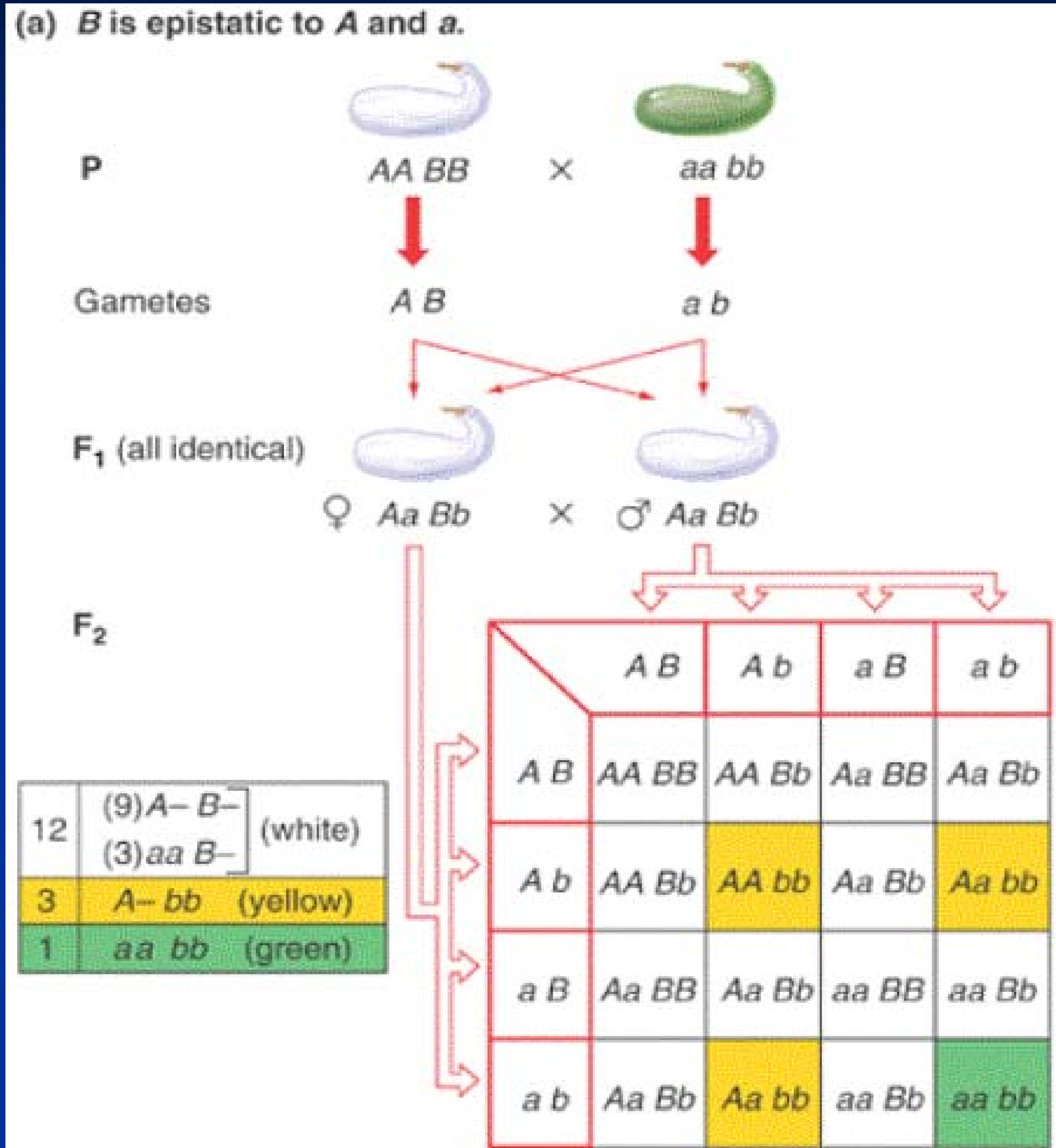
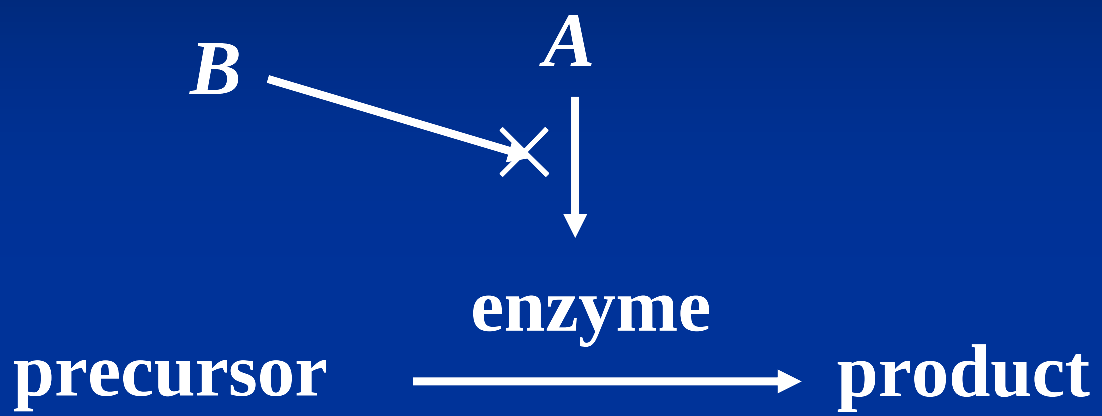


Fig. 3.15a

3-3 Dominant epistasis (II)

One gene inhibit the other gene's function



B **gene suppress** ***A*** **gene's function.**

Example：　Primrose color

A**：yellow**

B**：inhibit** ***A*****，white（colorless）**

P *AAbb* × *aaBB*

F_1 *AaBb*

Predicted F_2 ratio	Genotype	Phenotype	Final ratio
3/16	*A_bb*	yellow	3/16
9/16	*A_B_*	white	13/16
3/16	*aaB_*	white	
1/16	*aa bb*	white	

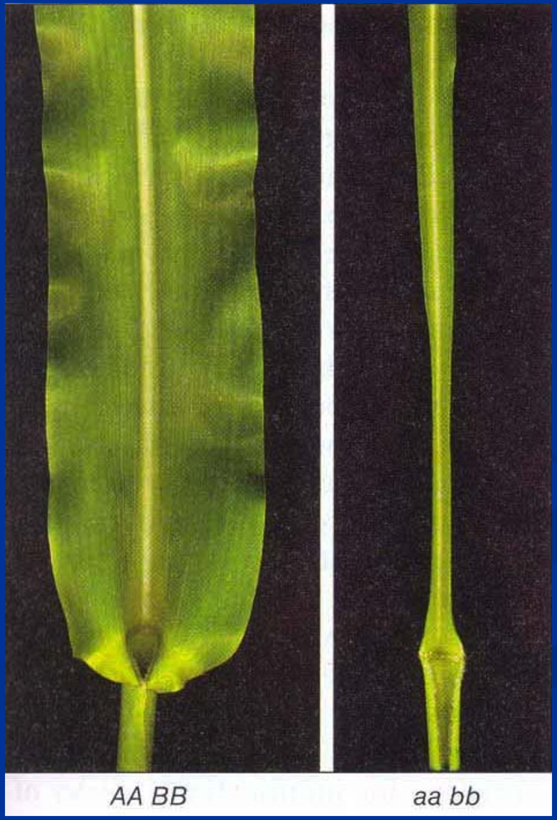
4. Two genes have the same phenotype

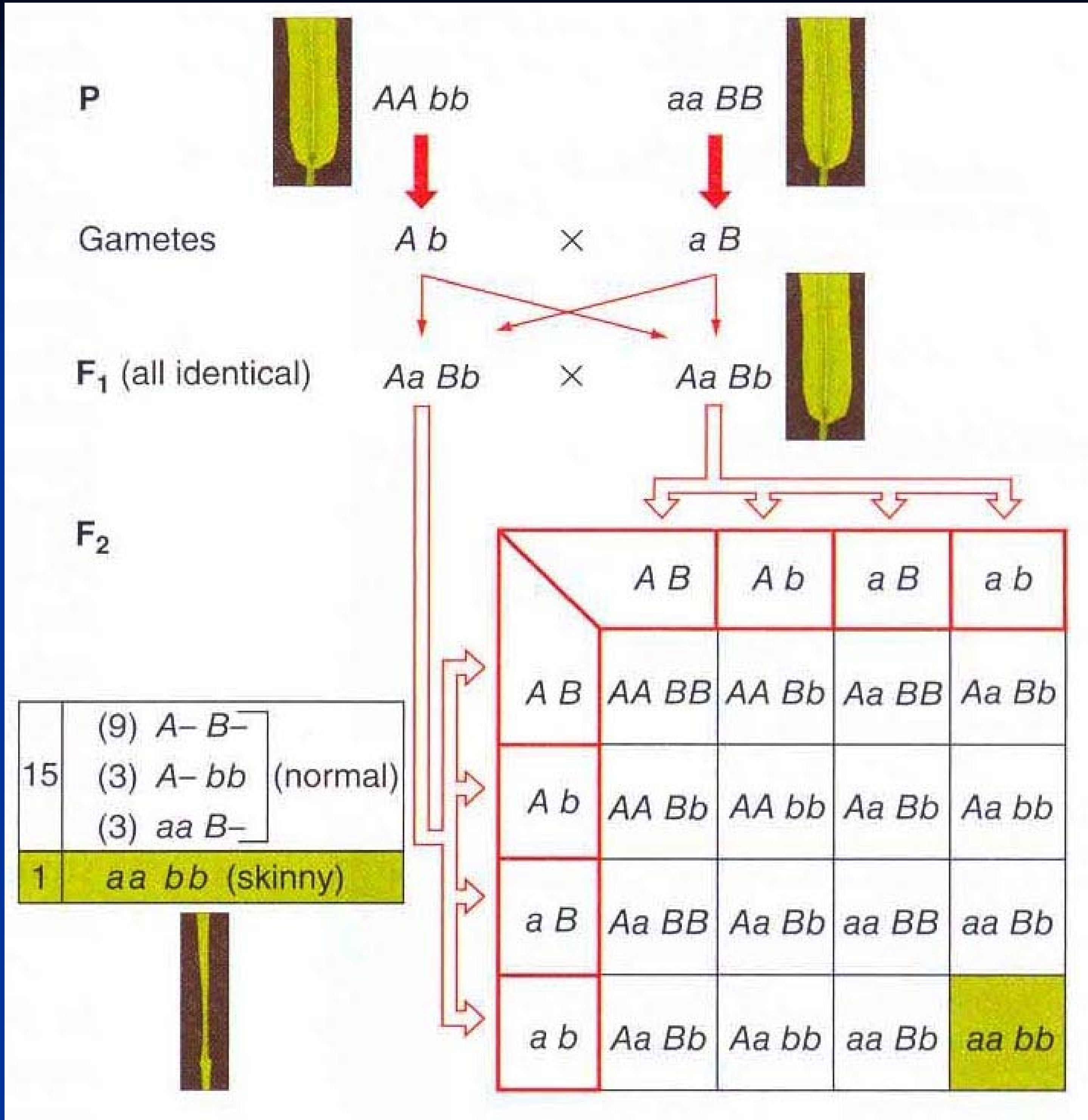
Precursor —*A* or *B*→ Product

A and *B* gene have the same function， only one is enough.

Example:

The shape of maize leaves.




P
AA bb
aa BB
Gametes
A b × a B
F1 (all identical)
Aa Bb × Aa Bb
F2
A B
A b
a B
a b
A B
AA BB
AA Bb
Aa BB
Aa Bb
A b
AA Bb
AA bb
Aa Bb
Aa bb
a B
Aa BB
Aa Bb
aa BB
aa Bb
a b
Aa Bb
Aa bb
aa Bb
aa bb
15
(9) A– B–
(3) A– bb
(3) aa B–
(normal)
1
aa bb (skinny)

P *AABB* × *aabb*

F1 ♀ *AaBb* × ♂ *AaBb*

F2

	AB	*Ab*	*aB*	*ab*
AB	*AABB*	*AABb*	*AaBB*	*AaBb*
Ab	*AABb*	*AAbb*	*AaBb*	*Aabb*
aB	*AbBB*	*AaBb*	*aaBB*	*aaBb*
ab	*AaBb*	*Aabb*	*aaBb*	*aabb*

9 *A_ B_*

3 *A_ bb*

3 *aa B_*

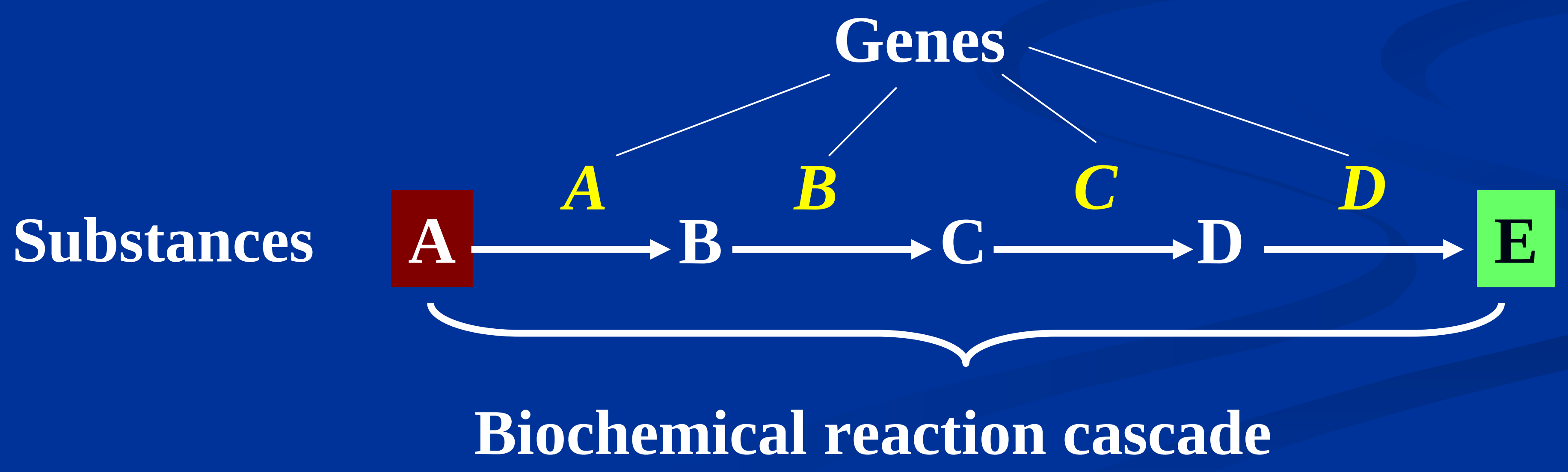
1 *aa bb*

TABLE 3.2 Summary of Gene Interactions

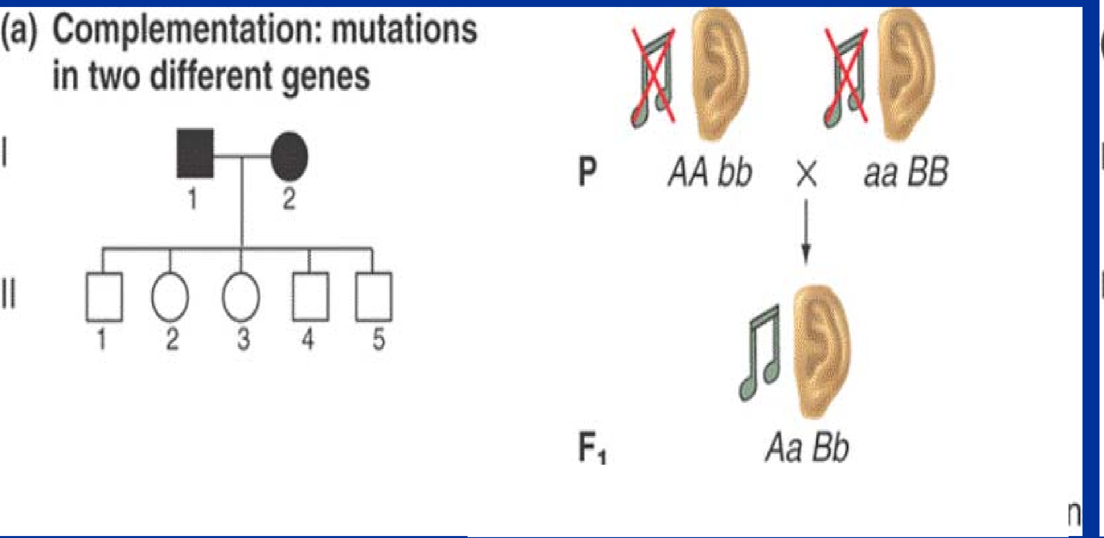
Gene Interaction	Example	F_2 Genotypic Ratios from an F_1 Dihybrid Cross: *A– B–*	*A– bb*	*aa B–*	*aa bb*	F_2 Phenotypic Ratio
None: Four distinct F_2 phenotypes	Lentil: seed coat color (see Fig. 3.10a)	9	3	3	1	9:3:3:1
Complementary: One dominant allele of each of two genes is necessary to produce phenotype	Sweet pea: flower color (see Fig. 3.12b)	9	3	3	1	9:7
Recessive epistasis: Homozygous recessive of one gene masks both alleles of another gene	Labrador retriever: coat color (see Fig. 3.14b)	9	3	3	1	9:3:4
Dominant epistasis I: Dominant allele of one gene hides effects of both alleles of another gene	Summer squash: color (see Fig. 3.17a)	9	3	3	1	12:3:1
Dominant epistasis II: Dominant allele of one gene hides effects of dominant allele of other gene	Chicken feathers: color (see Fig. 3.18a)	9	3	3	1	13:3
Redundancy: Only one dominant allele of either of two genes is necessary to produce phenotype	Maize: leaf development (see Fig. 3.19b)	9	3	3	1	15:1

5. Several genes can contribute to the same trait

- **Heterogeneous traits** are traits determined by a number of different genes. A mutation at any one of these genes can give rise to the same phenotype.
  - Albinism in plants, animals and humans.
  - Deafness in humans is a heterogeneous trait. About 50 different genes have mutant alleles that can cause deafness.



- **Difficult to determine which of many genes mutated in a person with a heterogeneous mutant phenotype.**
- **Complementation testing can determine if mutations arise from the same or different genes.**



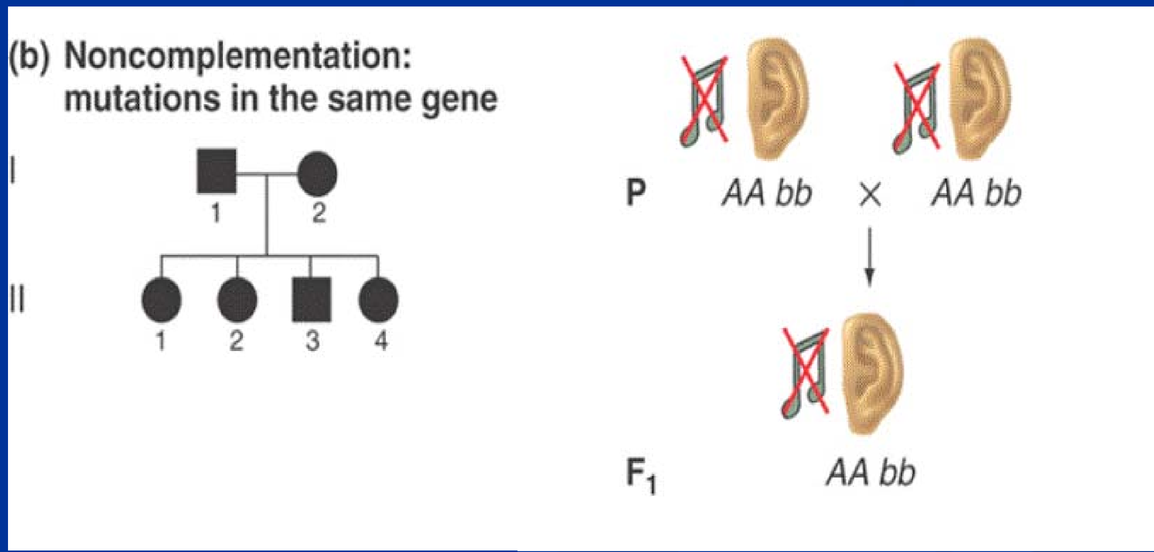


Fig. 3.16

Breeding studies help determine how a trait is inherited

- How do we know if a trait is caused by one gene or two genes that interact?
  - Ratios such as 9:7 or 13:3 can indicate potential gene interaction.
  - Further breeding studies can confirm hypotheses.

Testing two gene and one gene hypothesis – example from mice

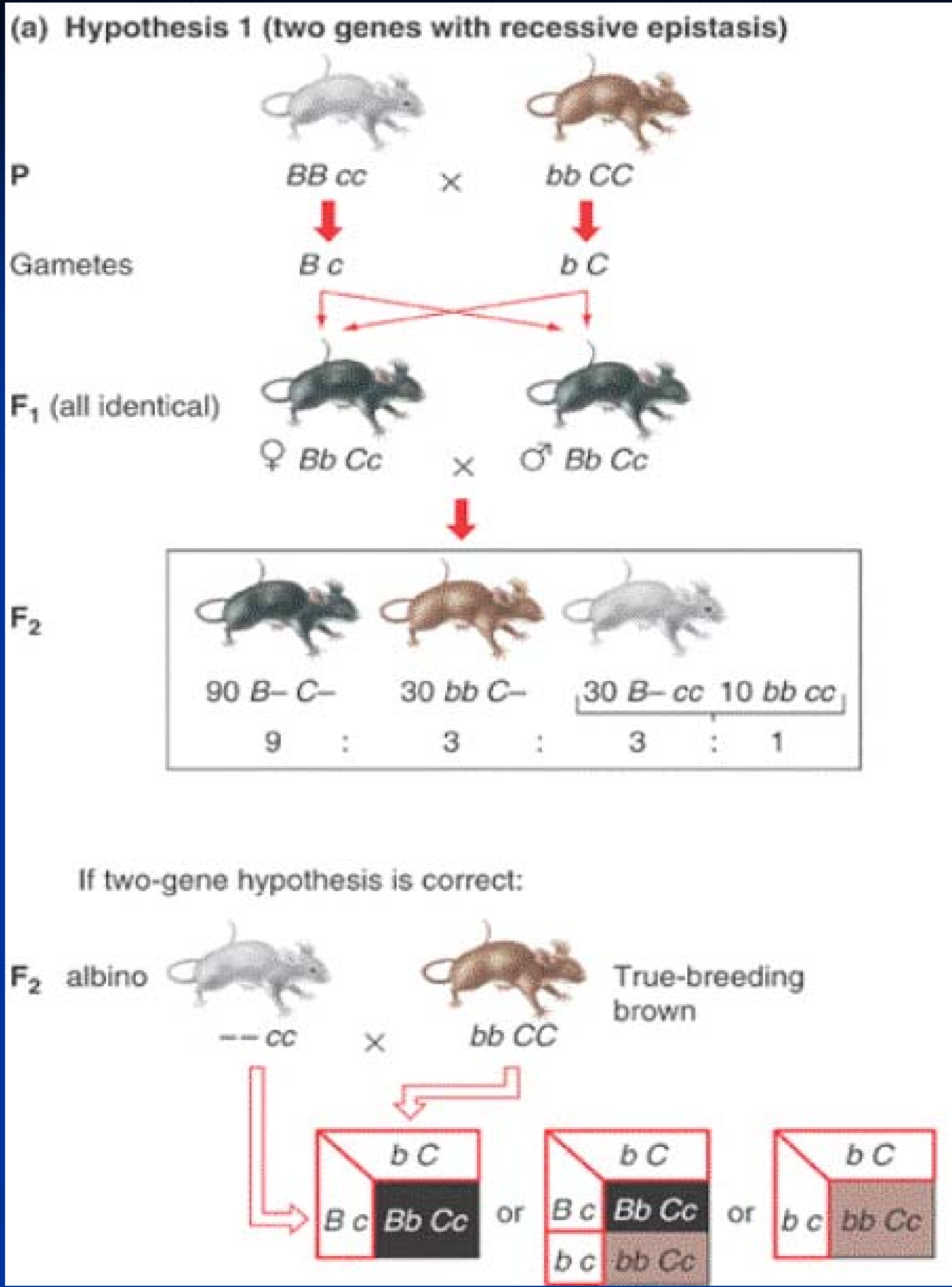


Fig. 3.18a

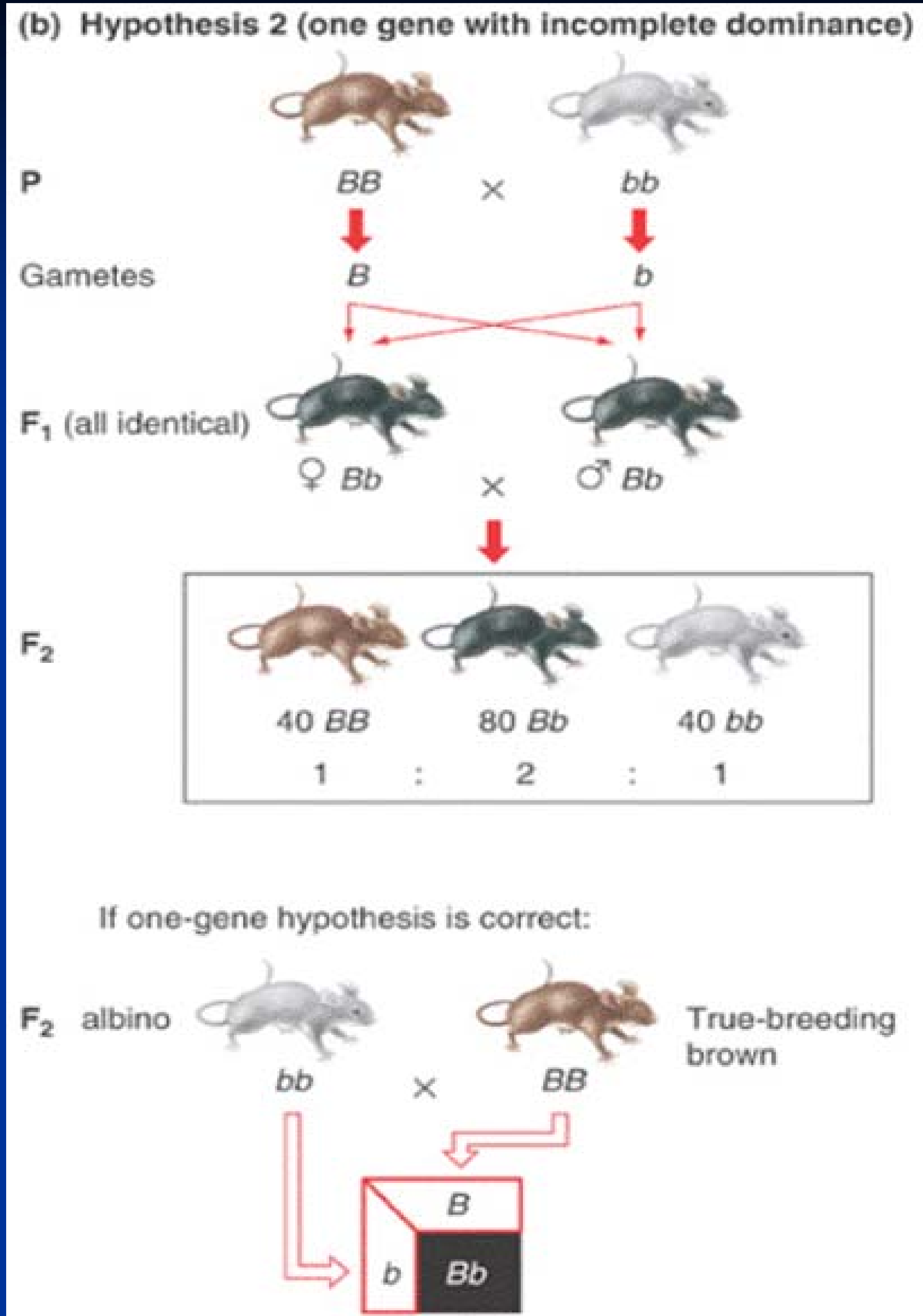

(b) Hypothesis 2 (one gene with incomplete dominance)
P
BB
×
bb
Gametes
B
b
F1 (all identical)
♀ Bb
×
♂ Bb
F2
40 BB
80 Bb
40 bb
1 : 2 : 1
If one-gene hypothesis is correct:
F2 albino
bb
×
BB
True-breeding brown
B
b
Bb

Fig. 3.18b

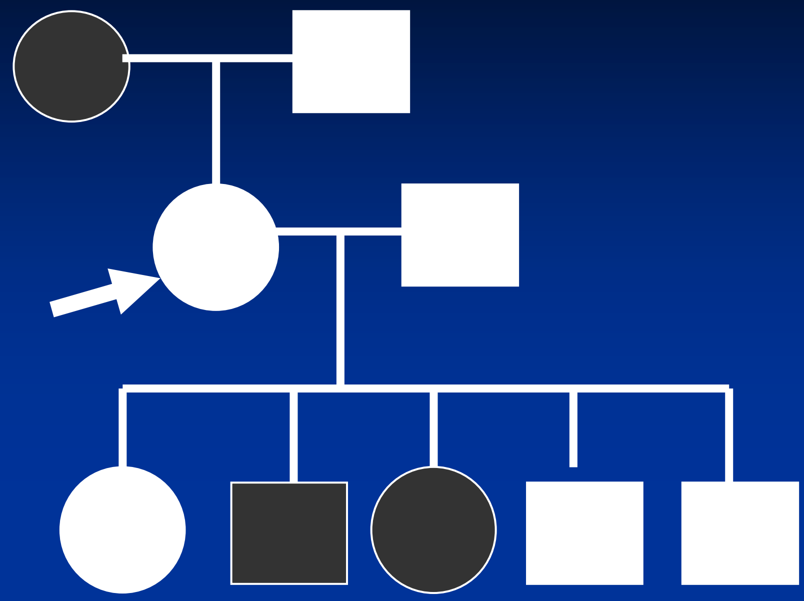
Summary of genetic variations on multifactorial traits

- Genes can interact to generate new phenotypes.
- The dominant alleles of two interacting genes can both be necessary for producing a phenotype.
- One gene's alleles can mask the effects of another gene's.
- Mutants alleles at one of two or more different genes can result in the same phenotype.

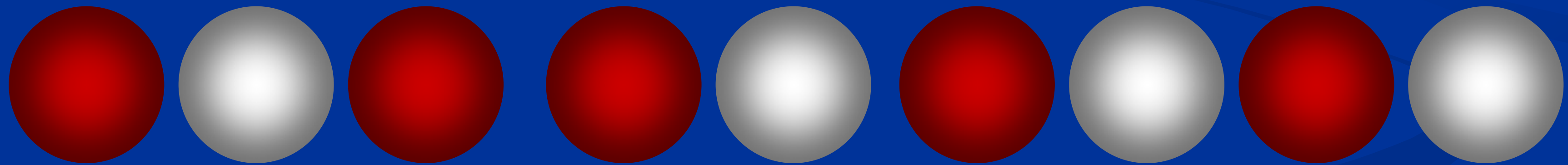
The same genotype does not always produce the same phenotype

- Phenotype often depends on penetrance and expressivity.
  - Penetrance (外显率): Percentage of individuals with a particular genotype that show the expected phenotype in a population.
    - Penetrance can be complete (100%) or incomplete (retinoblastoma 75%).
  - Expressivity (表现度): Degree or intensity with which a particular genotype is expressed in a phenotype
    - Expressivity can be variable or unvarying.

Incomplete penetrance

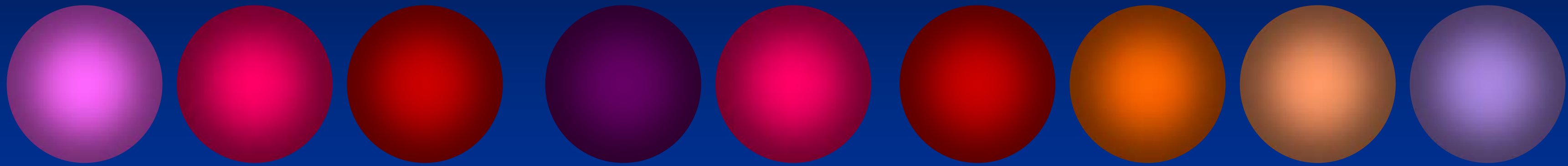


Phenotypic expression
(each circle represents an individual)



Variable penetrance

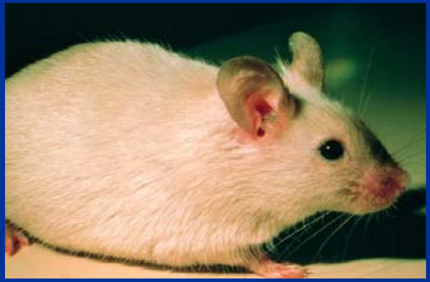
Variable expressivity



Color spots in beagle

- **Modifier genes have subtle, secondary effect on a phenotype from a major gene.**
- **Environment can affect the phenotypic expression of a genotype.**
  - **Temperature**
    - **Coat color in Siamese cats is lighter in its extremities.**
    - **Conditional lethals**
      - ***shibire* gene in fly is lethal at temperatures above 29^{o}C.**

Temperature can affect coat color



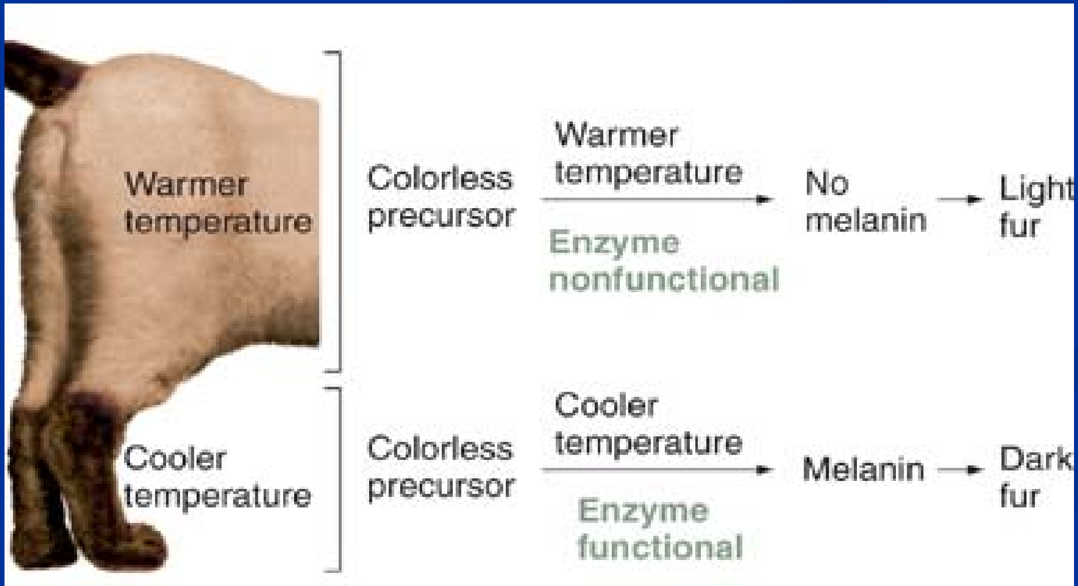


Fig. 3.20

- Environment can affect the phenotypic expression of a genotype.
  - Temperature
    - Coat color in Siamese cats is lighter in its extremities.
    - Conditional lethals
      - *shibire* gene in fly is lethal at temperatures above 29^{o}C.
  - Phenocopy (表型模拟): Change in phenotype arising from environmental agents that mimics the effect of a mutation at a gene.
    - In early 1960s, the drug thalidomide disrupts limb development in normal fetuses.
    - Diet, exercise, smoking contribute to certain heart and lung diseases.

Continuous variation can be explained by Mendelian analysis

- **Discontinuous traits**: Phenotype is clear cut without variation.
- **Continuous traits (连续性状)**: Phenotype shows continuous variation.

Height is a continuous trait in humans

Fig. 3.21a

Skin color is a continuous trait

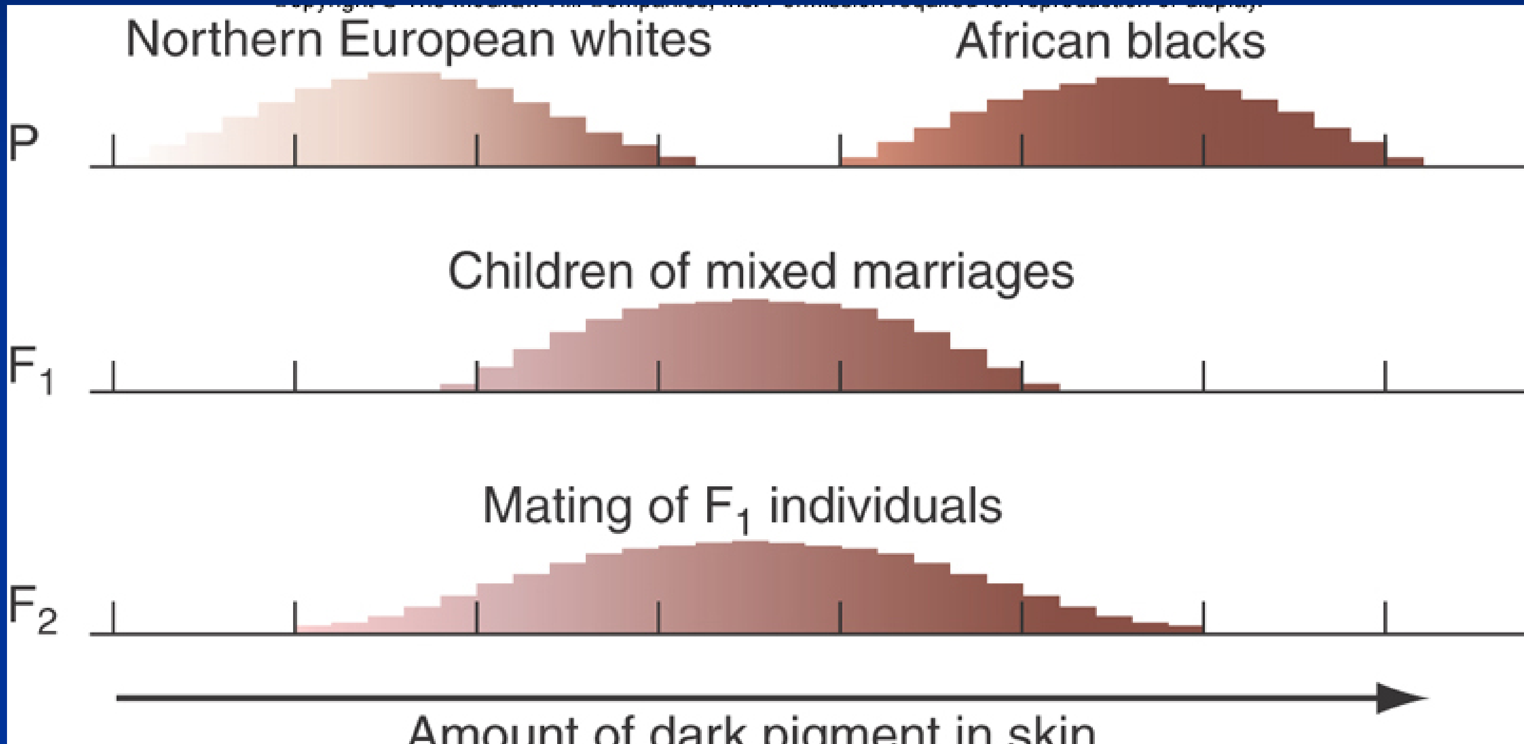


Fig. 3.21b

- **Continuous traits**: Phenotype shows continuous variation.
  - Continuous traits are also called **quantitative traits** by geneticists and are usually polygenic.
  - Continuous traits such as height in humans are determined by segregating alleles of many genes interacting with one another and the environment.
  - The more genes that contribute to a trait, the greater the number of possible phenotypic classes and the greater the similarity to continuous variation.