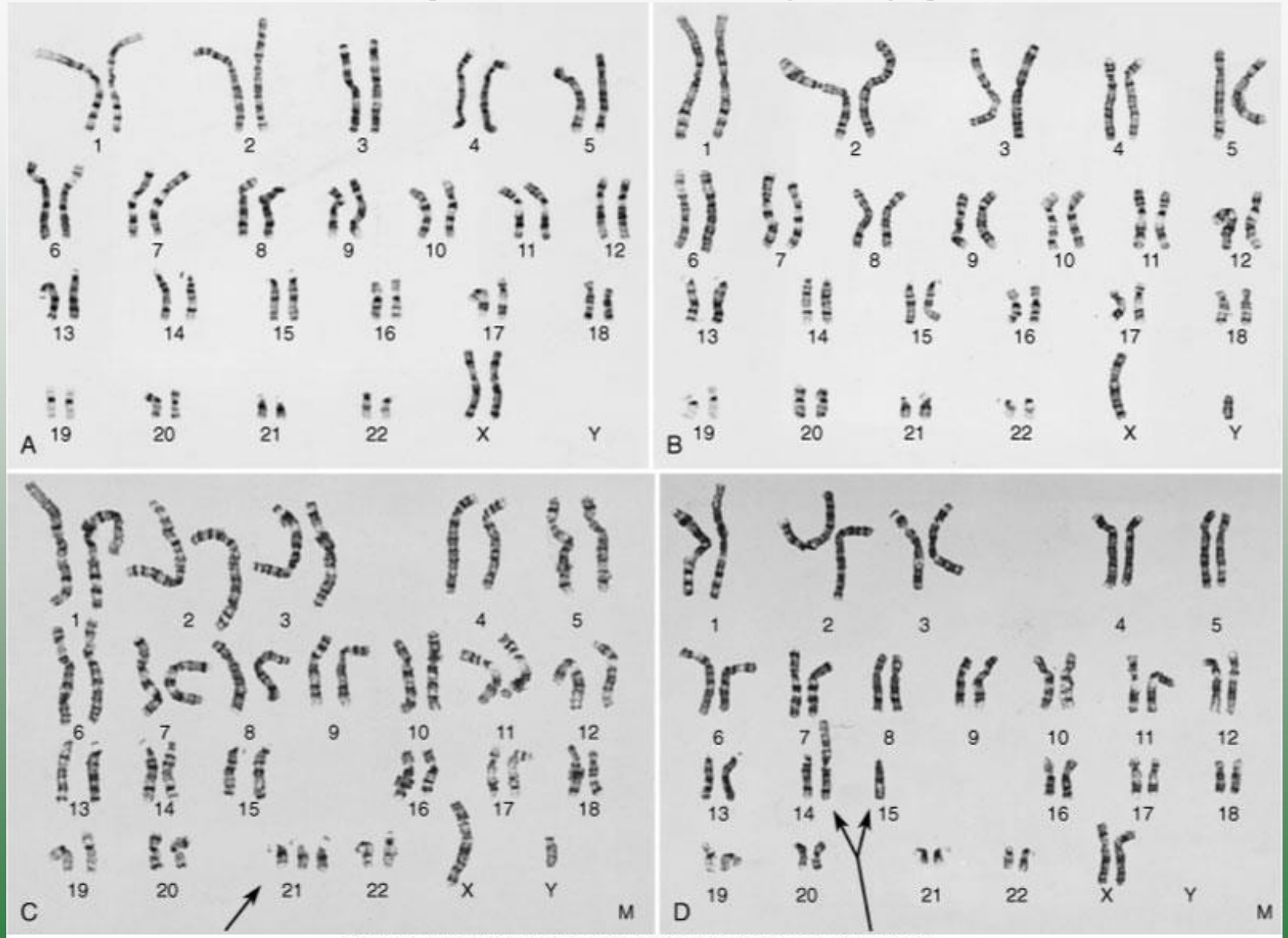
Chapter 21

Congenital and Genetic Disorders

Genetic Control

- Genetic information stored in chromosomes
  - 23 pairs in humans
  - 22 pairs—autosomes
  - One pair of sex chromosomes—XX or XY
  - Karyotype
    - Visual representation of chromosomes arranged in order of size
    - Used in diagnosis of chromosomal disorders

Examples of Karyotypes



Courtesy of Cytogenetics Laboratory, North York General Hospital, Toronto, Ontario, Canada.

Genetic Control (Cont.)

- Genotype
  - Actual genetic information carried by the individual
  - All cells except the gametes of an individual have the same genotype.
  - Not all genes are expressed in all cells.
- Phenotype
  - Expression of genes
  - Appearance of the individual's characteristics

Congenital Disorders

- Disorders present at birth
  - Include inherited or developmental disorders
- Inherited disorders may be caused by
  - Single-gene expression
    - (recessive / dominant)
  - Chromosomal defect
    - (monosomy, trisomy, translocations)
  - Polygenic expression
    - Multiple genes must be damaged to produce disease.

Congenital Disorders (Cont.)

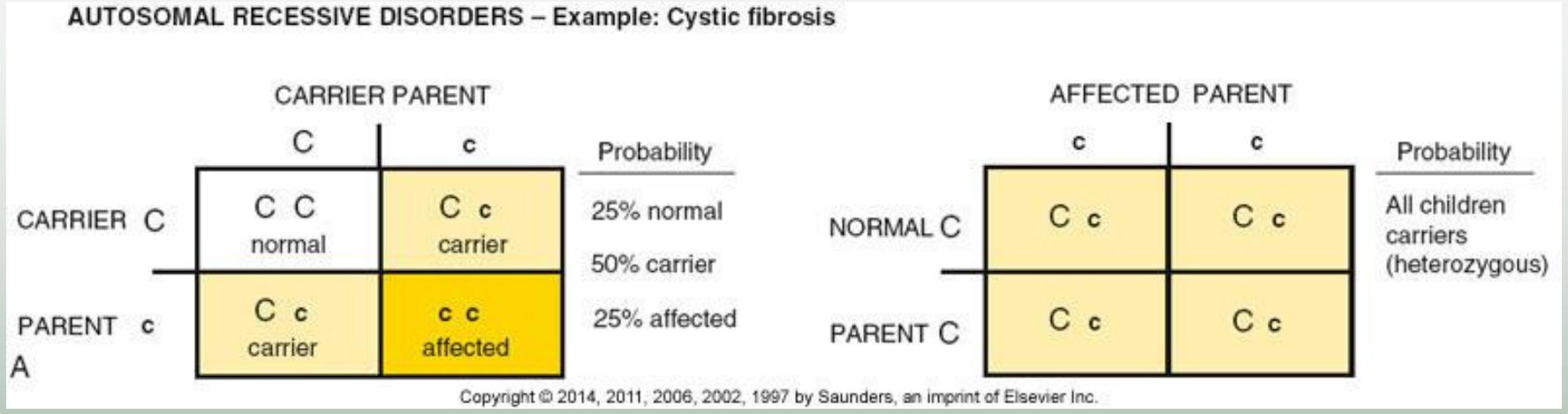
- Teratogenic agents
  - Agents that cause damage during embryonic or fetal development and produce a dysmorphic fetus.

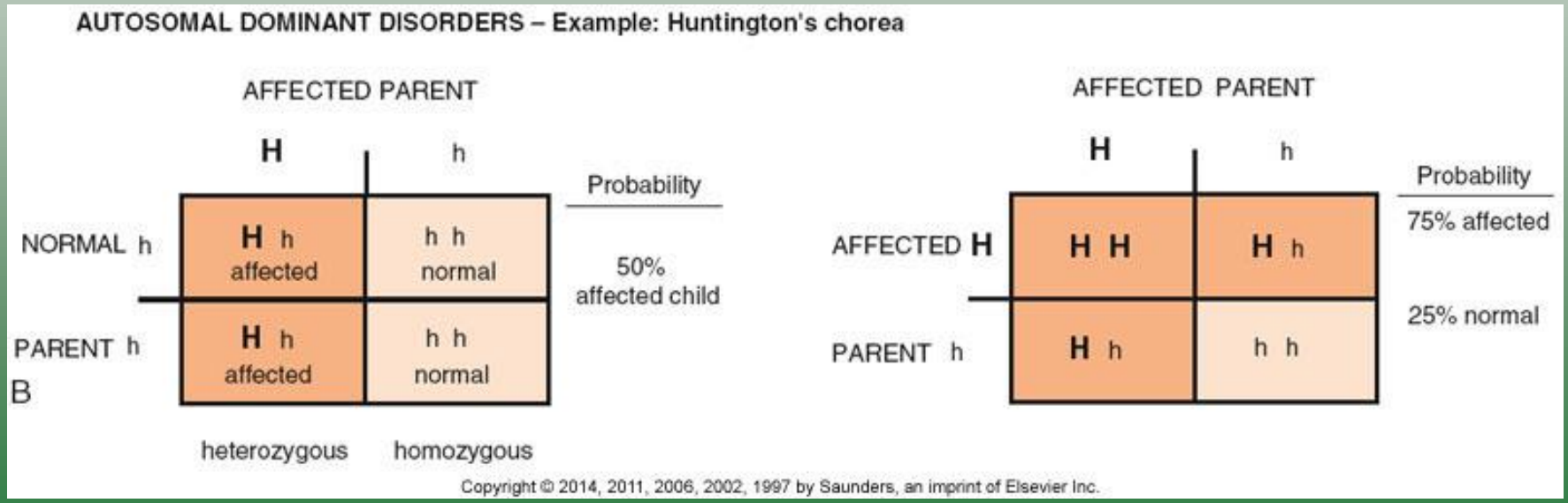
- Polygenic - Multifactorial disorders
  - Large number of disorders are of this type
  - Often have pattern of familial inheritance
  - Environmental component
    - Example: Diabetes – Diet.
    - Asthma – allergens in environment.

Congenital Disorders (Cont.)

- Other congenital or developmental disorders
  - Result from premature birth
  - Difficult labor and delivery
  - Cerebral palsy is an example.

(Punnett Square – Single Gene Defects)





Autosomal Recessive Disorders

- Cystic fibrosis
- PKU
- Tay-Sachs disease

Autosomal Dominant Disorders

- Adult polycystic kidney disease
- Huntington’s disease
- Familial hypercholesterolemia
- Marfan’s syndrome

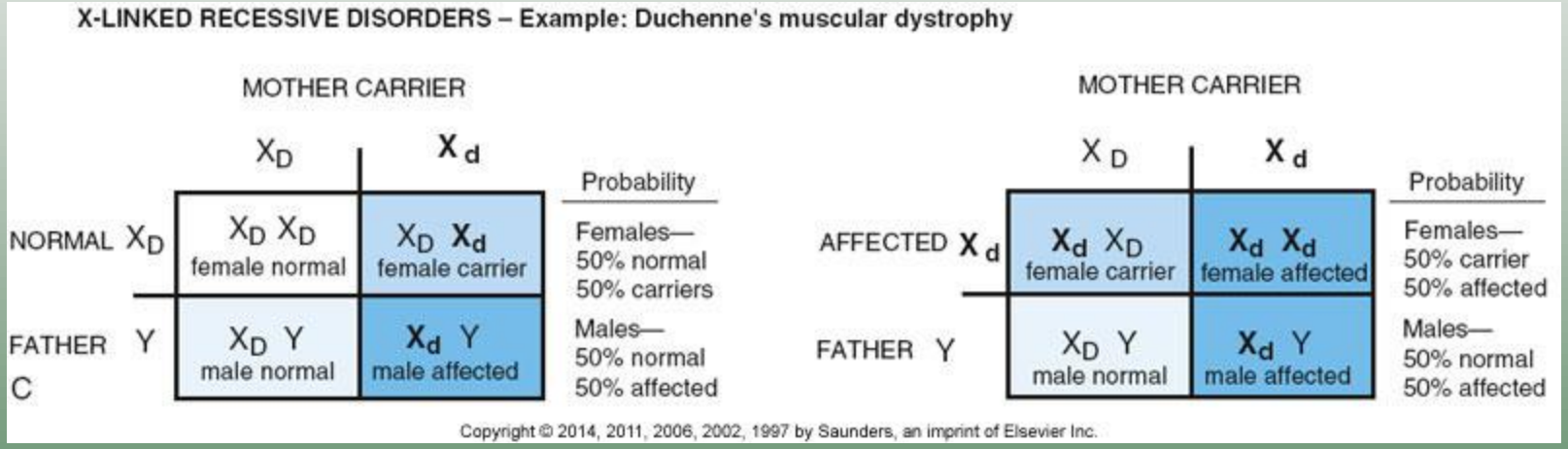
X-Linked Disorders

- Recessive
  - Allele carried on the X chromosome but not the Y chromosome
  - Manifested in all males because they have only one X chromosome.
  - Heterozygous females are carriers.
  - Homozygous recessive females may be affected.
  - Inheritance may appear to skip generations.
  - Examples:
    - Duchenne muscular dystrophy
    - Classic hemophilia

X-Linked Disorders (Cont.)

- Dominant disorder
  - Heterozygous males and females affected
  - Reduced penetrance in females
  - Fragile X syndrome is an example.
    - Most common genetic cause of cognitive deficits
    - Effects are variable and related to the extent of mutation of the allele.

X-Linked Recessive Disorder (Punnett Square)



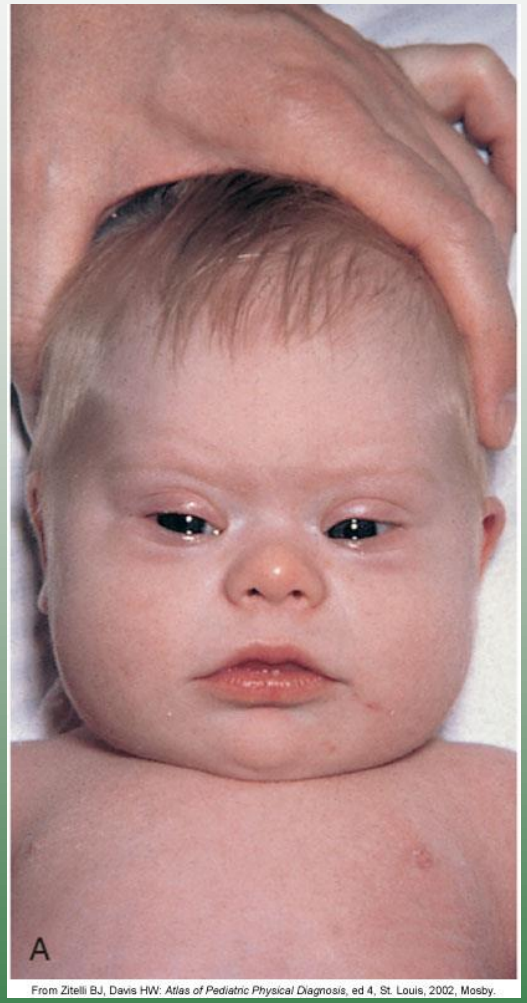
Chromosomal Disorders

- Down syndrome
  - Trisomy 21
  - May be caused by nondisjunction or translocation
- Turner syndrome XO
  - Affects females
  - Short stature
  - Infertility
- Klinefelter syndrome XXY
  - Extra X chromosome is present
  - Infertility

Down Syndrome

- Trisomy 21
- Common chromosomal disorder
  - Affects physical and mental development
- Risk increases with maternal age
- Triple or quad screening test and/or first-trimester screening test (ultrasound + maternal blood screening)
  - May be used to screen for risk of Down syndrome
  - Amniocentesis or chorionic villi sampling used to confirm the disorder prior to birth

Characteristics of Down Syndrome



From Zitelli BJ, Davis HW: *Atlas of Pediatric Physical Diagnosis*, ed 4, St. Louis, 2002, Mosby.

- Small head, round face, flat facial profile
- Slanted eyes and epicanthic fold
- Large tongue, high-arched palate
- Small hands, single palmar crease
- Short stature
- Muscles tend to be hypotonic; loose joints
- Delayed developmental stages
- Cognitive impairment ranges from mild to major
- Delayed or incomplete sexual development
  - Males infertile
  - Females have lower rate of conception

Developmental Disorders

- Exposure to drugs, chemicals, or radiation during childbearing years
- Exposure to known teratogens in the first 2 months of development
  - Impairs organogenesis
- TORCH—acronym for maternal infections that can result in anomalies
  - Routine prenatal screening tests

Diagnostic Tools

- Testing may be available.
  - Prior to conception
  - During first trimester of pregnancy
  - In newborn
- Testing recommended for:
  - Family history of a specific disease
  - Previous birth to child with abnormality
  - Ethnic groups with high risk for specific disease
  - Pregnant women > 35 years of age

Diagnostic Tools (Cont.)

- Blood tests of pregnant woman
  - Alpha-fetoprotein testing
- In utero testing
  - Amniocentesis
  - Chorionic villi assay
- Neonatal testing
  - Excreted metabolites (e.g., PKU)
  - Blood testing

Genetic Engineering

- Isolating, copying, and transplanting genes
  - In microorganisms, plants, animals, humans
  - Used in agriculture to produce transgenic or genetically modified foods
- Ultimate goal
  - Insert normally functioning allele to prevent disease
  - Technically possible but clinical trials have not been uniformly successful

Gene Therapy

- Identifies gene and protein responsible for condition
- Determines how gene expression is controlled
- Produces drug that will inhibit gene expression
- Research focus on cancer growth promoters has resulted in these types of drugs.

Genetic Screening and DNA Testing

- Screening at-risk populations for a specific allele
  - Costly
  - Concerns regarding privacy and access to information
- DNA testing to identify individuals for paternity or forensic purposes
- Legislation has been drafted in the United States to protect the genetic rights of individuals.
  - Health care
  - Employment
  - Insurance