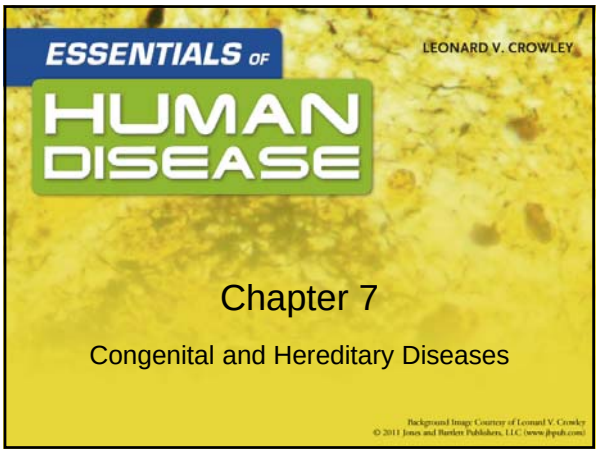


Learning Objectives (1 of 2)

- Describe
  - Common causes of congenital malformations and their incidence
  - Abnormalities of sex chromosomes and manifestations
  - Common genetic abnormalities and transmission
- Compare phenylketonuria versus hemophilia in terms of transmission and clinical manifestations
- Describe congenital malformations resulting from uterine injury

Learning Objectives (2 of 2)

- Explain
  - Amniocentesis
  - Multifactorial inheritance
  - Example of multifactorial defect and relevant factors
- List causes and clinical manifestations of Down syndrome
- Discuss reasons for identifying 14/21 chromosome translocation carrier
- Explain methods for diagnosing congenital abnormalities.

Hereditary and Congenital Malformations

- Congenital disease: abnormality present at birth, even though it may not be detected until some time after birth
- Hereditary or genetic disease: resulting from a chromosome abnormality or a defective gene

Genetics (1 of 2)

- Chromosomes: composed of double coils of DNA
- Genes: segments of DNA chains
- Genome: sum total of all genes contained in a cell's chromosomes; the same in all cells
- In human beings, normal chromosome component:
  - 22 pairs of autosomes
  - 1 pair of sex chromosomes (XX in females and XY in males)
- Karyotype: a representation of a person's set of chromosomes

Genetics (2 of 2)

- In somatic cells: chromosomes exist in pairs, one member of each pair is derived from male parent and other from female parent
  - With 22 pairs called autosomes
  - Except for the sex chromosomes, members of the pair are similar in size, shape, and appearance (homologous chromosomes)
- Mitosis: cell division of somatic cells
  - Each of two new cells or daughter cells receives the same chromosomes as the parent cell

Factors in Congenital Malformations

- Genetic or hereditary disorders or diseases caused by abnormalities in an individual's genetic material (genome)
- Congenital disease or malformation: any abnormality present at birth
- Four factors in congenital malformations
  1. Chromosomal abnormalities
  2. Abnormalities of individual genes
  3. Intrauterine injury to embryo or fetus
  4. Environmental factors

Causes of Congenital Malformations

- 2-3% of all newborn infants have congenital defects
- Additional 2-3% defects: NOT recognized at birth; developmental defects demonstrated later as infants grow older
- 25% to 50% spontaneously aborted embryos, fetuses, and stillborn infants have major malformations

Chromosomal Abnormalities

- Nondisjunction: failure of homologous chromosomes in germ cells to separate in first or second meiotic division
  - May involve either sex chromosomes or autosomes
  - Causes abnormalities in distribution of chromosomes between germ cells
  - One of two germ cells has an extra chromosome while the other lacks a chromosome

Chromosomal Abnormalities

- Monosomy: absence of a chromosome in a cell
- Trisomy: presence of an extra chromosome in a cell
- Deletions: chromosome breaks during meiosis and broken piece is lost
- Translocations: misplaced chromosome or part of it attaches to another chromosome

Sex Chromosome Abnormalities (1 of 3)

- Variations in normal number of sex chromosomes are often associated with some reduction of intelligence
  - Y chromosome: directs masculine sexual differentiation, associated with male body configuration regardless of number of X chromosomes present
  - Extra Y: no significant effect as it mainly carries genes concerned with male sexual differentiation
  - Absent Y: body configuration is female
  - Extra X in female: has little effect (one X chromosome is inactivated)
  - Extra X in male: has adverse effects on male development

Sex Chromosome Abnormalities (2 of 3)

- Two most common ones in the female
  - 1. Turner's Syndrome: absence of one X chromosome
  - 2. Triple X Syndrome: extra X chromosome
- Two most common ones in the male
  - 1. Klinefelter's Syndrome: extra X chromosome
  - 2. XYY Syndrome: extra Y chromosome

Sex Chromosome Abnormalities (3 of 3)

- Fragile X Syndrome (x-linked mental deficiency)
- Not related to either excess or deficiency of sex chromosomes
- Associated with a characteristic abnormality of the X chromosome
- Second to Down syndrome as a major cause of mental deficiency

Syndromes resulting from an abnormal complement of sex chromosomes

	USUAL GENOTYPE	APPROXIMATE INCIDENCE	UNUSUAL NUMBER OF BARR BODIES	UNUSUAL NUMBER OF Y FLUORESCENT BODIES	FERTILITY
Turner's syndrome	45,X	1:2500 females	0	0	Sterile
Triple X syndrome	47,XXX	1:850 males	2	0	Usually not impaired
Klinefelter's syndrome	47,XXY	1:750 males	1	1	Usually sterile
XYY syndrome	47,XYY	1:850 males	0	2	Usually not impaired

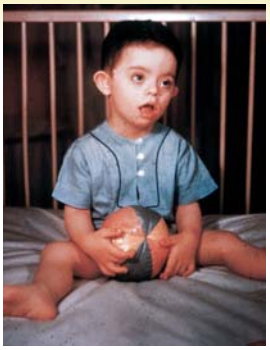
Autosomal Abnormalities (1 of 2)

- Absence of an autosome results in the loss of several genes so that development is generally not possible and the embryo is aborted.
- Deletion of a small part of an autosome may be compatible with development but usually results in multiple severe congenital abnormalities.
- **Down syndrome: most common chromosomal abnormality**, an autosomal trisomy

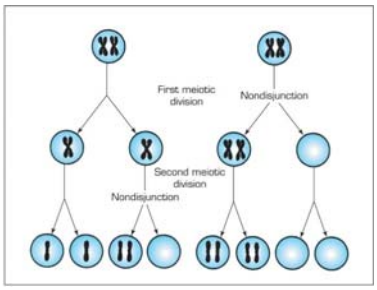
Autosomal Abnormalities (2 of 2)

- With trisomy of small chromosome 21
- Many fetuses are aborted early in pregnancy (70%)
- Those who live have Down syndrome
  - Nondisjunction during oogenesis occurs in 95% of cases
- Increased frequency with advancing maternal age: 1 in 50 if mother is > 40 years old
- Extra chromosome 21 acquired as part of the translocation chromosome

Down Syndrome



Effects of nondisjunction in meiosis, leading to formation of gametes with an extra or missing chromosome.



Translocation Down syndrome (1 of 4)

- Occurs in small number of persons with Down syndrome
- Extra chromosome: chromosome 21 fused with chromosome 14 or another chromosome
- Total number of chromosomes not increased but genetic material is equivalent to 47 chromosomes

Translocation Down syndrome (2 of 4)

- Causes
  - Normal chromosomes in cells of both parents
    - Translocation occurred accidentally during gametogenesis in the germ cells of one of the parents
  - 14/21 carrier in one of the parents
    - Carrier parent has only 45 chromosomes because one is the fusion of chromosome 21 with 14

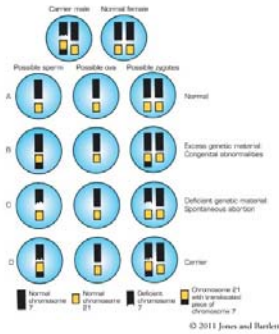
Translocation Down syndrome (3 of 4)

- 14/21 carrier in one of the parents
- Carrier parent is capable of transmitting abnormal chromosome to his or her children resulting in translocation Down syndrome

Translocation Down syndrome (4 of 4)

- Possible outcomes of pregnancy involving a female carrier
  - Translocation chromosome is not always transmitted
  - Normal
  - Carrier
  - Nonviable
  - Down Syndrome

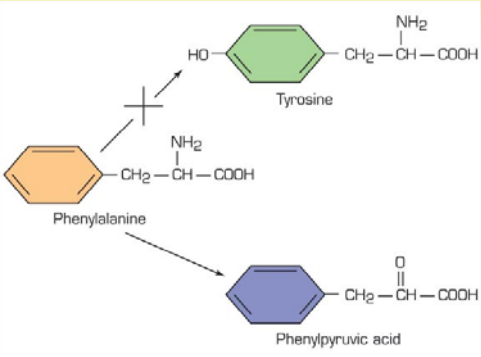
Possible offspring produced when one parent is a carrier of a chromosome translocation.



Transmission of Genetically Determined Diseases

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- Codominant inheritance
- X-linked inheritance
- Most hereditary diseases are transmitted on autosomes
- Few are carried on sex chromosomes

Metabolic defects in phenylketonuria.



Intrauterine Injury

- Causes
  - Harmful drugs and chemicals (Table 9-3)
  - Radiation
  - Maternal infections (Figure 9-11)
    - Rubella, cytomegalovirus, *Toxoplasma gondii*
    - 3rd–8th week after conception: embryo is most vulnerable to injury as organ systems are forming

Categories of Drugs Harmful to Fetus (Table 6-3)

A: No risk to fetus demonstrated in well-controlled studies in humans

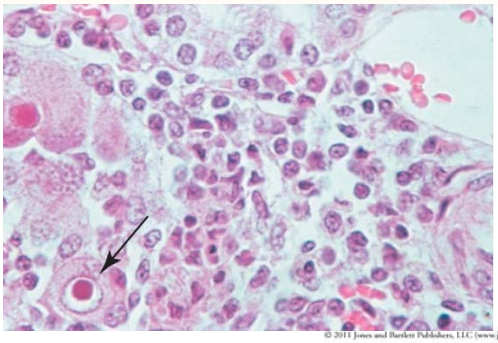
B: No evidence of risk to fetus. Either animal studies show risk but human studies do not or there are no adequate human studies by animal studies do not indicate risk.

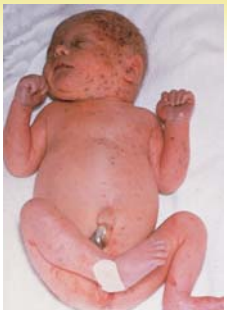
C: Risk to fetus cannot be rules out. No human studies available to assess risk. Animal studies either are not available or indicate possible risk.

D: Positive evidence of risk to fetur; however, drug is needed to treat patients, and no safer alternative drug is available. Potential benefit to patients outweighs risk to fetus.

X: Absolutely contraindicated in pregnancy. Severe risk to fetus greatly outweights any possible benefit to patients.

Characteristic appearance of kidney cells infected by cytomegalovirus. High magnification view.





Cytomegalovirus infection in newborn

Multifactorial Inheritance

- Combined effect of multiple genes interacting with environmental agents
- Congenital abnormalities
  - Cleft lip, cleft palate, cardiac malformations, clubfoot, dislocation of hip, anencephaly, spina bifida

Prenatal Diagnosis of Congenital Abnormalities (1 of 2)

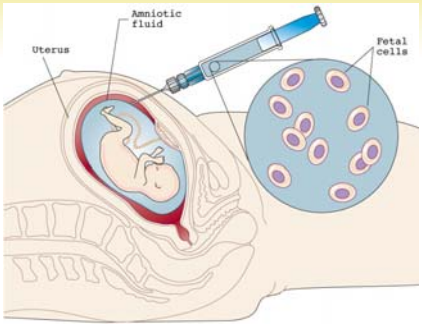
- Examination of fetal cells: determination of biochemical abnormalities in fetal cells
  - Chromosomal abnormalities
  - Biochemical abnormalities
  - Analysis of DNA
- Examination of amnionic fluid: products secreted into fluid by fetus that may indicate fetal abnormality

Prenatal Diagnosis of Congenital Abnormalities (2 of 2)

- Ultrasound examination: detection of major structural abnormalities
  - Major structural abnormalities of nervous system (anencephaly; spina bifida)
  - Hydrocephalus
  - Obstruction of urinary tract
  - Failure of kidneys to develop
  - Failure of limbs to form normally
- Fetal DNA analysis: determination of biochemical abnormalities by analysis of DNA of fetal cells
  - Amniocentesis
  - Chorionic villus sampling

Amniocentesis

- Alpha fetoprotein: high concentration in amniotic fluid is suggestive of a neural tube defect
- Amniotic fluid for study: transabdominal amniocentesis
  - Usually performed between the 14th and 18th week of pregnancy
  - Primary use: prenatal detection of chromosomal abnormality
  - Screening offered to all women, but most important for women over age 35 due to higher incidence of Down syndrome in infants born to older women



Amniocentesis

Indications for Amniocentesis

1. Maternal age over 35 years
2. Previous infant born with Down syndrome or other chromosomal abnormality
3. Known translocation chromosome carrier, or other chromosome abnormality in either parent
4. Risk of fetal genetic disease that can be detected by fetal cell biochemical or DNA analysis
5. Maternal blood tests (triple screen) indicating increased risk of fetal chromosome abnormality

Chorionic Villus Sampling (1 of 2)

- Chorionic villi: frond-like structures that form part of placenta and attach to lining of uterus
  - Fetal cells are obtained for evaluation using chorionic villi sample
  - Amniotic fluid not used for analysis
  - Small catheter inserted through cervix to the site where villi are attached on the uterus
  - Small area is suctioned

Chorionic Villus Sampling (2 of 2)

- Advantages
  - Can be performed earlier than amniocentesis (8th to 10th week)
  - Carries less risk from abortion if parent decides to terminate pregnancy in case of congenital abnormality
- Disadvantages
  - More difficult technically than amniocentesis
  - Complications: spontaneous abortion, limb deformities in fetus

Discussion

- What are the consequences of chromosome nondisjunction? What is Down syndrome?
- What is amniocentesis? How is it used in prenatal diagnosis of congenital malformations?