1 **Notion of Cause**
- how to identify
- correlation vs. causation
- difficult to study
  - various reporting method
  - not identified at birth
  - difficult to perform prospective studies
  - limitations of retrospective studies

2 **Two Theoretical Notions**
- endogenous factors
- exogenous factors
- combination of both

3 **Etiology**
- 6 different etiologies
  - Genetic
  - Chromosomal
  - Mechanical
  - Sporadic
  - unknown
  - Teratologic

4 **Heredity and Clefting**
- Classic Study, Fogh-Anderson, 1942
- studied 703 patients and families
- looked at family history

5 **Conclusions**
- clefting ran in families; inheritance was a factor in 37% of prepalatal and palatal clefts: 19% of cases in palatal clefts alone.
- two different malformations: prepalatal and palatal
- sex distribution differences: males: cl & cp: females: cp alone
- twin data: 37% concordance with monozygotic twins

6 **Genetic Inheritance**
- 1866: experiments of Gregor Mendel, Australian Monk
- identified patterns of inheritance
- did not know mechanism; now implicate genes

7 **What do genes do?**
- Submicroscopic; perform two functions
1. Morphogenesis: contain basic set of instructions for human
   - regulates formations of specific cell types, cell functions and distribution of cells.
2. Sequence of nucleotide bases: stretch of DNA that codes for a protein
   - Regulates function, growth and development after birth

**8 Genetic Mutation**
- Error in genetic code may result in birth defect
- Abnormal gene – mutant: any alteration in the gene sequence
- Mutant: 10-15% of birth anomalies
  - Code has been changed in some way
    - Deletion
    - Addition
    - Noncoding material (entron)

**9 Diagnosis of genetic error**
- Clinical diagnosis: I.e., Marfan Syndrome
- Biochemical essay: PKU
- DNA analysis: direct analysis of mutant gene

**10 Patterns of Inheritance: Single Gene disorder**
- Based on Mendelian Model
- Disorders may be either autosomal or X-linked
  - Autosomal - the gene is on autosome
  - X-linked - the gene is on the X Chromo
- Dominant - presence of 1 mutant gene sufficient
- Recessive - requires 2 abnormal genes

**11 Autosomal Dominant**
- If dominant gene is mutant, child will inherit disorder
- One parent has dominant gene, 50% chance of inheriting this gene

**12 Autosomal Dominant Disorders**
- Majority of syndromes that include c/lp are autosomal dominant
- Examples: Van der Woude lip pits, Sticklers, treacher Collins, Apert, EEC, Polydactyly, Huntington, Neurofibromatosis

**13 Autosomal Recessive**
- Mutant gene from both parents
- Child: 25% chance of 2 normal genes
  - 50% chance: one normal, one mutant; trait not expressed
  - 25% chance two mutant genes; trait will be expressed

**14 Autosomal Recessive Disorders**
- 1/3rd of all syndromes with clefting
- Cystic Fibrosis: 1/1600
Sickle Cell Anemia
Tay Sachs Disease
PKU

15 ☐ X-Linked
- x-linked recessive affect only males
- one X chromo, mutant - adverse effect
- Mom is carrier, 50% chance boy affected; 0% girl affected

16 ☐ X-Linked Disorders
- red/green color blindness
- hemophilia
- Duchenne muscular dystrophy,
- agammaglobulinemia

17 ☐ Multifactorial Inheritance Pattern
- proposed with identification of noncompliance with Mendelian Patterns of Inheritance
- proposes interaction of genotype with environmental factors
- Features:
  - defect in single system
  - broad range of severity
  - no predictable pattern of recurrence

18 ☐ Multifactorial Support
- based on issues relating to patterns of recurrence
- genetic basis for clefting based on F-A data: however, accounts for only @ 35%.
- Other 2/3rds of clefting noted as "solitary": no family history

19 ☐ Twin Data
- monozygotic twins: predict 100% concordance if genetic
- actual: 35-42%
- dizygotic twins: 7%