Objectives for this Chapter

A student reading this chapter will be able to:

1. Discuss and define the concepts of environment and disease.
2. List and explain the factors influencing environmental disease including infectious disease, physical and chemical injury, ionizing radiation, developmental disease, neoplastic disease, and nutritional disease.
3. Explain the process of genetic replication in mammalian cells. List the major genetic components and discuss their primary actions and features.
4. Describe and discuss the major mechanisms of developmental and genetic diseases.
Objectives for this Chapter

5. Describe and provide a schematic of the new processes in recombinant-DNA and genetic screening techniques.

6. Discuss and describe the new concepts on the origins of cancer, risk factors, and current trends.

LIVING WITH THE EARTH

Introduction

We continue to manufacture and disperse billions of tons of over 70,000 potentially toxic chemicals into the biosphere without regard for nature or an appreciation of the danger that these chemicals can bring to our earth or to us.

LIVING WITH THE EARTH

Love Canal: Declared an emergency in 1978

- William Love 1892 canal to produce power
- Board of education built schools, private homes, and complaints ensued from 1950s
- NY State Commissioner: Edwin Vukadin
- Lois Marie Gibbs - Center for Environmental Health and Justice

- Times Beach Missouri: Dioxin contamination discovered in 1982
- A Civil Action 1980s
- Anne Anderson, Jan Schlictmann

- Woburn
**LIVING WITH THE EARTH**

**ENVIRONMENTAL DISEASE**

**Introduction**

- Carcinogen
  - Any chemical known to cause cancer.
  - Nearly 90 percent of cancers can be traced to an environmental cause and so may be largely preventable.

What are the messages given through the public media about toxic chemicals?

- Exposure to toxic chemicals have dramatically increased the risk of cancer.
- Common household and agricultural chemicals are causing many human diseases and death.

What are the messages given through the public media about toxic chemicals?

- Polluted air and water are major sources of disease risk.
- Environmental chemicals are interfering with the reproductive process in humans and producing harmful effects in the fetus and young children.

Thalidomide
Defining the Term Environment in Relation to Disease (Cancer)

- Environment
  - Personal and cultural behavior including smoking, diet, alcohol consumption, sexual and reproductive patterns, workplace, infections, food additives, and pollution along with the strictly physical environment.
  - Dr. John Higginson founder and director of the WHO of research on Cancer
  - Nearly 2/3 of cancer have an environmental cause

Some of the Major Factors associated with Cancer

- Diet
- Tobacco
- Infection
- Sexual behavior
- Occupation

Fig. 4.1

Adapted from Morbidity and Mortality Weekly Report
Pollution

Pollution may be defined as the presence of a foreign substance - organic, inorganic, radiological or biological - that tends to degrade the quality of the environment so as to create a health hazard.

Defining Disease

A definite pathological process having a characteristic set of signs and symptoms which are detrimental to the well-being of the individual.

Disease Terminology

- Endemic
  - Diseases that already exist in a community where it is maintained in a low but constant incidence.
- Epidemic
  - Marked increase in incidence of disease within limited area affecting ever-increasing number of people.
Disease Terminology

• Pandemic
  – An epidemic spread throughout the world, as in the case of various outbreaks of influenza.

Disease Terminology

• Acute Disease
  – Having a rapid onset, is usually self-limiting, and are of relatively short duration.

• Chronic Disease
  – Having a slow onset and lasting for extended period of time. (i.e. cancer, emphysema, some forms of heart disease, or AIDS)

Defining Disease

• Infectious Disease
  – Infectious diseases result from the pathologic process occurring when a microbial agent invades the body.
Infectious Disease

• Reservoirs
  – Sources of disease which can be living organisms or inanimate objects that provide the conditions where the organisms may survive, multiply, and also provide the conditions necessary for transmission.

Infectious Disease

• Carriers
  – People who may or may not exhibit symptoms, but harbor and transmit the disease organisms.

• Zoonoses
  – Diseases that are spread from animals to humans, such as Lyme Disease.

Infectious Disease

• Major Routes of Infection
  – Contact
  – Vehicles
  – Vectors
Major Routes of infection

- **Contact**
  - Direct Contact Transmission (person-to-person)
  - Indirect Contact Transmission (cups, needles)
  - Droplet Infections (sneezing, coughing; droplets travel less than one meter)

Major Routes of infection

- **Vehicle**
  - Disease agents that are transmitted by various media such as air, water, food, intravenous fluids or blood, and drugs.

Major Routes of infection

- **Vectors**
  - Animals that carry pathogens from one host to another, either from another human that is infected or from an infected animal.
**Major Routes of infection**

- **Vectors**
  - Mechanical Transmission (foot pads)
  - Biological Transmission (biting insects and agent reproduces in vector)

- **Types of Hosts**
  - Definitive Host (sexual cycle of disease agent takes place in definitive host - mosquito for malaria)
  - Intermediate Host (asexual cycle - humans for malaria)

**Physical and Chemical Injury**

- **Physical Injuries**
  - Mechanical Injury
  - Thermal Injury
  - Ionizing Radiation

- **Major mechanisms for chemical Injury are:**
  - Interference with enzyme activity (cyanide)
  - Directly combining with some cell component other than enzymes (CO)
  - Producing a secondary action in which a chemical causes the release or formation of a more harmful substance (allergens)
Developmental Disease

Every individual within each species is very much a representation of the information contained in the genome together with the expression of those genes in the development of that individual.

Developmental Disease

Developmental disease occurs when faults or mistakes occur within the genes (or chromosomes), or stages in development of the fetus are disturbed.

Major Categories of genetic disease include:
- Single gene defects
- Cytogenic defects
Developmental Disease

- Cytogenic Defects are:
  - Abnormalities in the number or structure of chromosomes
- Teratologic Defects are:
  - Defects which arise during the embryonic period of development. Causative factors are usually not genetic but from exposure to chemicals or radiation (teratogens)

Neoplastic Disease

- Neoplasia
  - The new and uncontrolled growth of abnormal tissue from the transformation of normal body cells.
- Tumors
  - The growth of cells as a result of neoplasia, also called a neoplasm.
  - Tumors may be malignant or benign.

Malignant Tumors

- Exogenous Factors-arising from the environment
  - Habits (tobacco use, poor nutrition, alcohol use, sexual and reproductive activities)
  - Ionizing radiation
  - Chemical exposure
  - Environment (socio-economic, geographical, and occupational)
  - Oncogenic viruses
Malignant Tumors

- Endogenous Factors-originating from within the body
  - Gender
  - Age
  - Hormonal imbalance
  - Impaired immune system
  - Genetic predisposition

Nutritional Disease

- Malnutrition, as a consequence of inadequate diet, is often associated with ignorance and poverty which are manifestations of a weakened society.

Nutritional Disease

- Kwashiorkor
  - Caused by a lack of protein in children 1-3 years old.
- Marasmus
  - Caused by lack of food in children one year of age.
- Scurvy
  - Caused by the lack of vitamin C.
Environmental Disease

Any pathologic process having a characteristic set of signs and symptoms which are detrimental to the well-being of the individual and are the consequence of external factors, including exposure to physical or chemical agents, poor nutrition, and social or cultural behaviors.

THE ROLE OF GENETICS IN DISEASE

• Structure and Function
  – This thread of life is deoxyribonucleic acid (DNA), a spiral, staircase-shaped molecule over 3 billion steps long compressed in the nucleus of living cells.
  – The storage and transcription of biological information occurs within DNA which has the power to express that biological information in the form of proteins.

Structure and Function

– DNA is located within the cell nucleus of each of the human body’s 100 trillion cells (except mature red blood cells) (Fig. 4-2).
– Each nucleus contains 46 chromosomes arranged in 23 homologous pairs.
Structure and Function of DNA

- DNA is a very long, thread-like molecule which is formed by four recurring subunits called mononucleotides.
- Nucleotides are identical and attached to each other in a long chain by phosphodiester links between carbon atoms in each molecule (Fig. 4-3).
Structure and Function of DNA

- Four different recurring mononucleotides are the base elements of the DNA coding system (Fig. 4-4).
  - Adenine and Guanine (purines)
  - Thymine and cytosine (pyrimidines)

Structure and Function of DNA

- Pair nucleotide bases fit together in a precise way, held together by hydrogen bonds between the base pairs and by hydrophobic bonding (Fig. 4-4).
**Replication**

- Dividing cells provide each daughter cell with one complementary strand of the parent DNA and then synthesize a complementary strand to produce double-stranded DNA.

**Structure and Function of DNA**

- **Proteins**
  - Proteins are composed of specific sequences of amino acids linked by peptide bonds
- **Enzymes are proteins**
  - Proteins that interact with a substrate much like a key in a lock to catalyze the formation of a new molecule or product.

**Protein Biosynthesis**

- DNA must first be transcribed to another molecule called messenger RNA or mRNA before it can reach the ribosomes outside of the cell.
Protein Biosynthesis

• Codons
  – A group of 3 nucleotide bases which specifies the position of one amino acid in a protein molecule.

• Anticodons
  – The recognition site for specific codon triplet (Fig. 4-5).

Fig. 4-5

Diseases of Genetics and Development

• Genetic Abnormalities
  – Mutation
    • A change in the nucleotide base sequence of DNA.
Genetic Abnormalities

- Many human diseases are associated with genetic defects (Fig. 4-6).
  - Single-gene defects known as point mutations or base substitutions.
  - Cytogenetic defects are abnormalities in the number or structure of chromosomes.

Spontaneous Mutation
- Point mutations that occur spontaneously because of occasional mistakes created in the process of DNA replication without any intervention of external factors.

Mutagens
- Agents in the environment including chemicals or radiation that promote mutations.
Genetic Abnormalities

• Dominant Genes
  – The genes are always expressed phenotypically (physical appearance). (Huntington’s disease) (Woody Guthrie)

• Co-dominant Genes
  – Partly expressed if present as a single allele. (Sickle cell disease)

• Recessive Genes
  – A defective gene must occur in both chromosomes at complementary sites in order for the disease to be expressed. (PKU, cystic fibrosis)

• Cytogenetic Defects
  – Abnormalities in the number or structure of the chromosomes. (Trisomy 21)

Teratologic diseases

• Exposure during embryonic development
  - Accutane
  - Alcohol
  - Cigarette smoke
  - Diethylstilbestrol
  - Thalidomide
  - German measles
  - Toxoplasmosis
  - Absence of folic acid (vitamin B)
New Approaches in Genetics

- Methods of Studying Genes
  - Genetic Engineering is the science of creating recombinant DNA, which permits the transfer of genes between unrelated species.

Methods of Studying Genes

- Restriction enzymes are enzymes used to cut DNA into several predictable and reportable pieces (Fig. 4-7).
- Insulin is genetically engineered using restriction enzymes and cloning vectors (plasmids) (Fig. 4-8).

Fig. 4-7

Adapted from Tortora et al.
Methods of Studying Genes

- In addition to making products, recombinant-DNA technology can produce millions of exact copies (cloning) useful in analytic techniques such as hybridization (Fig. 4-9), or genetic screening (Fig. 4-10).
Genechip technology has greatly simplified this task. This single-use probe array has thousands of different oligonucleotide probes.

**The Hunt for Environmental Genes**

- Sarin nerve gas attack by Shinnyo cult members in Tokyo subway (1995) revealed variations in genes coding for paraoxonase enzyme. Ten percent of Caucasians and 25% of Asians produce enzyme that is 10X better at detoxifying paraoxonase.
- Variations in genes coding for P450 and NAT genes can increase cancer bladder risk 6X in smokers.

**The Promise of Genetic Therapy**

- Gene therapy may involve removing cells with defective genes from a person and replacing those genes with normal or healthy genes and then placing the cells back into the patient.
The Ethical Dilemma

- The discovery of defective genes is progressing at a much faster pace than the development of other treatments and gives rise to many ethical and legal dilemmas.

CANCER – WHAT IS IT?

- Most cancers develop from the interaction of genetics with environment and perhaps less than five percent can be attributed to hereditary factors alone (Fig. 4-11).

CANCER – WHAT IS IT?

- Cancer produces its damaging effects through:
  - local damaging effects;
  - metastasis; and
  - systemic effects.
CANCER – WHAT IS IT?

- Metastasis
  - A process where malignancies travel producing tumors at distant sites.

How Does Cancer Develop?

- In a typical pathway leading to cancer, a chemical agent combines with human DNA to form an adduct (carcinogenic residues bound to DNA) which leads to increased mutations that may eventually accumulate and lead to cancer.

Fig. 4-11

Adapted from Perera. 10
How Does Cancer Develop?

• Oncogenes
  – Defective genes that produce proteins that inappropriately stimulate cell division.

• Spell-checker proteins
  – When DNA is replicated, spell-checker proteins correct errors in the DNA. If the Genes that code for these proteins are defective, the spell-checker does not function correctly (Fig. 4-12).

Fig. 4-12

Genes such as MSH2 and MSH6 code for proteins that correct errors in the order of nucleotides (DNA replication). These proteins are known as “spell-checker” proteins. Defective spell-checker proteins fail to correct errors. When such errors occur in genes controlling cell growth, a major step toward the development of a cancer cell occurs.
How Does Cancer Develop?

• Apoptosis
  – The process of cellular self-destruction when cell damage accumulates to the point where cell integrity is compromised.
  – One of the most important genes coding for enzymes involved in apoptosis is p53, a tumor suppression gene.

• Mutations occurring along the p53 gene appear at characteristic sites with unique base sequences known as biomarkers.
  – The p53 gene halts cell division until DNA can be repaired, or turns on the mechanism for cell destruction if repair is unlikely.

• Angiogenesis
  – The malignant cells grow into a small mass that develops nutrient-bearing blood vessels in a process called angiogenesis.
  – Recently, anti-angiogenesis compounds have been developed that prevent or reverse the formation of blood vessels in tumors of rats.
Major Cancer Risks

• Smoking
  – Smoking cigarettes causes more than 30 percent of all cancers in the United States.
  – Eighty eight percent of the 120,000 people newly diagnosed with lung cancer each year are smokers.

Major Cancer Risks

• Diet
  – High fat intake has been linked with increased risks to colon and prostate cancer, while being excessively overweight encourages the growth of endometrial cancer.

Major Cancer Risks

• Diet
  – Cruciferous vegetables including broccoli, cabbage, cauliflower, kale, and brussel sprouts all produce a powerful isothiocyanate anti-carcinogen known as sulforaphane
Major Cancer Risks

- Diet
  - Apoptosis may be triggered by butyric acid produced when bacteria ferment fiber in the gut.
  - Consumption of high fiber foods instead of refined flour and processed foods also appears to reduce the risk of cancer.

Trends in Cancer

- Data show that after increasing for 1.2 percent annually from 1973 to 1990, the rate of new cases (incidence) of 23 major cancers sites combined fell an average of 0.7 percent a year from 1990 to 1995 (Fig. 4-13).
Trends in Cancer

- NCI has reported that the rate of cancer among American children has been steadily rising nearly one percent per year.

Trends in Cancer

- Children tend to be more susceptible to environmental toxins because:
  - they take in more food, water, and air and accompanying carcinogens relative to body weight compared to adults;
  - nursing infants get higher exposures of substances such as dioxin in breast milk than adults exposed to background levels;
  - children have a higher internal dose of toxins and greater genetic damage than adults who have similar exposures to tobacco smoke and polycyclic aromatic hydrocarbons (PAH);
Trends in Cancer

- Children tend to be more susceptible to environmental toxins because:
  - children have reduced detoxification and repair systems;
  - they have a higher rate of cell proliferation during early developmental stages; and
  - children have increased absorption and retention of toxins.