3.3: Systemic Toxic Effects

Types of Systemic Toxic Effects

Toxic effects are generally categorized according to the site of the toxic effect. In some cases, the effect may occur at only one site. This site is termed the **specific target organ**.

In other cases, toxic effects may occur at multiple sites. This is known as **systemic toxicity**. Types of systemic toxicity include:

- Acute Toxicity
- Subchronic Toxicity
- Chronic Toxicity
- Carcinogenicity
- Developmental Toxicity
- Genetic Toxicity (somatic cells)

Acute Toxicity

Acute toxicity occurs almost immediately (seconds/minutes/hours/days) after an exposure. An **acute exposure** is usually a single dose or a series of doses received within a 24-hour period. Death can be a major concern in cases of acute exposures. For example:

- In 1989, 5,000 people died and 30,000 were permanently disabled due to exposure to methyl isocyanate from an industrial accident in India.
- Many people die each year from inhaling carbon monoxide from faulty heaters.

Figure 3.3.1. Faulty gas heaters can emit toxic carbon monoxide
(Image Source: iStock Photos, ©)

Subchronic Toxicity

Subchronic toxicity results from repeated exposure for several weeks or months. This is a common human exposure pattern for some pharmaceuticals and environmental agents. For example:

- Ingestion of warfarin (Coumadin®) tablets (blood thinners) for several weeks as a treatment for venous thrombosis can cause internal bleeding.
- Workplace exposure to lead over a period of several weeks can result in anemia.

Figure 3.3.2. Warfarin Tablets (left); old lead pipes (right)
(Image Source: iStock Photos, ©)

Chronic Toxicity

Chronic toxicity represents cumulative damage to specific organ systems and takes many months or years to become a recognizable clinical disease. Damage due to subclinical individual exposures may go unnoticed. With repeated exposures or long-term continual exposure, the damage from this type of exposure slowly builds up (cumulative damage) until the damage exceeds the threshold for chronic toxicity. Ultimately, the damage becomes so severe that the organ can no longer function normally and a variety of chronic toxic effects may result.

Chronic toxic effects include:

- Cirrhosis in alcoholics who have ingested ethanol for several years.
- Chronic kidney disease in workmen with several years of exposure to lead.
- Chronic bronchitis in long-term cigarette smokers.
- Pulmonary fibrosis in coal miners (black lung disease).

Figure 3.3.3. Smoking cigarettes and/or drinking alcohol over a long period of time can lead to chronic toxicity
(Image Source: iStock Photos, ©)

Carcinogenicity

Carcinogenicity is a **complex multistage process** of abnormal cell growth and differentiation that can lead to cancer. The two stages of carcinogenicity are:

1. **Initiation** — a normal cell undergoes irreversible changes.
2. **Promotion** — initiated cells are stimulated to progress to cancer.

Chemicals can act as **initiators** or **promoters**.

The initial transformation that causes normal cells to undergo irreversible changes results from the mutation of the cellular genes that control normal cell functions. The mutation may lead to abnormal cell growth. It may involve a loss of suppresser genes that usually restrict abnormal cell growth. Many other factors are involved, such as growth factors, immune suppression, and hormones.

A **tumor (neoplasm)** is simply an uncontrolled growth of cells:

- **Benign tumors** grow at the site of origin; do not invade adjacent tissues or metastasize; and generally are treatable.
- **Malignant tumors (cancer)** invade adjacent tissues or migrate to distant sites **(metastasis)**. They are more difficult to treat and often cause death.

Developmental Toxicity

Developmental toxicity pertains to adverse toxic effects to the developing embryo or fetus. It can result from toxicant exposure to either parent before conception or to the mother and her developing embryo or fetus. The three basic types of developmental toxicity are:

1. **Embryolethality** — failure to conceive, spontaneous abortion, or stillbirth.
2. **Embryotoxicity** — growth retardation or delayed growth of specific organ systems.
3. **Teratogenicity** — irreversible conditions that leave permanent birth defects in live offspring, such as cleft palette or missing limbs.

Chemicals cause developmental toxicity in two ways:

1. They act directly on cells of the embryo, causing cell death or cell damage, leading to abnormal organ development.
2. They induce a mutation in a parent's germ cell, which is transmitted to the fertilized ovum. Some mutated fertilized ova develop into abnormal embryos.

Figure 3.3.4. Ultrasound images of a developing fetus
(Image Source: iStock Photos, ©)

Genetic Toxicity

Genetic toxicity results from damage to DNA and altered genetic expression. This process is known as **mutagenesis**. The genetic change is referred to as a **mutation** and the agent causing the change is called a **mutagen**. There are three types of genetic changes:

1. **Gene mutation** — change in DNA sequence within a gene.
2. **Chromosome aberration** — changes in the chromosome structure.
3. **Aneuploidy** or **polyploidy** — increase or decrease in number of chromosomes.

If the mutation occurs in a germ cell, the effect is **heritable**. This means there is no effect on the exposed person; rather, the effect is passed on to future generations.

If the mutation occurs in a **somatic** cell, it can cause altered cell growth (for example, cancer) or cell death (for example, teratogenesis) in the exposed person.

Figure 3.3.5. Genetic toxicity results from damage to DNA and altered genetic expression
(Image Source: iStock Photos, ©)