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**QUESTIONS.**

1. What do you understand by primary or simple obesity?
2. How does congenital syndrome and drug therapy affect obesity?
3. Outline the etiology of cancer and its molecular basis.

**ANSWERS.**

1. Simple obesity also known as primary obesity is due to excess energy intake and too little consumption, also known as diet induced obesity and has the largest proportions in all types of obesity (95%). It is caused by the intake of high fat or high density diets. It is not associated with any clinical conditions. It is caused mainly by intake of excessive food and lack of exercise. When an individual consumes high amounts of energy, particularly fat and sugars, but does not burn off the energy through exercise and physical activity, much of the surplus energy will be stored by the body as fat; this causes simple obesity.
2. ETIOLOGY OF CANCER.

The majority of cancers, some 90–95% of cases, are due to genetic mutations from environmental and lifestyle factors. The remaining 5–10% are due to inherited genetics. Environmental refers to any cause that is not inherited genetically, such as lifestyle, economic, and behavioral factors and not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), lack of physical activity, and pollution. Psychological stress does not appear to be a risk factor for the onset of cancer, though it may worsen outcomes in those who already have cancer. The main causes of cancer are listed below:

a).Chemicals.

Exposure to particular substances have been linked to specific types of cancer. These substances are called carcinogens. Tobacco smoke, for example, causes 90% of lung cancer. It also causes cancer in the larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in five cancer deaths worldwide and about one in three in the developed world.

In Western Europe, 10% of cancers in males and 3% of cancers in females are attributed to alcohol exposure, especially liver and digestive tract cancers. Cancer from work-related substance exposures may cause between 2 and 20% of cases, causing at least 200,000 deaths. Cancers such as lung cancer and mesothelioma can come from inhaling tobacco smoke or asbestos fibers, or leukemia from exposure to benzene.

b). Diet and exercise.

Diet, physical inactivity and obesity are related to up to 30–35% of cancer deaths. Excess body weight is associated with the development of many types of cancer. Physical inactivity is believed to contribute to cancer risk, not only through its effect on body weight but also through negative effects on the immune system and endocrine system. More than half of the effect from diet is due to over nutrition (eating too much), rather than from eating too few vegetables or other healthful foods.Some specific foods are linked to specific cancers. A high-salt diet is linked to gastric cancer. Aflatoxin B1, a frequent food contaminant, causes liver cancer. Betel nut chewing can cause oral cancer.

c). Infection.

Worldwide approximately 18% of cancer deaths are related to infectious diseases. Viruses are the usual infectious agents that cause cancer but cancer bacteria and parasites may also play a role. Oncoviruses (viruses that can cause cancer) include human papillomavirus (cervical cancer), Epstein–Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma) and human T-cell leukemia virus-1 (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma. Parasitic infections associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma).

d). Radiation.

Radiation exposure such as ultraviolet radiation and radioactive material is a risk factor for cancer. Many non-melanoma skin cancers are due to ultraviolet radiation, mostly from sunlight. Sources of ionizing radiation include medical imaging and radon gas. Ionizing radiation is not a particularly strong mutagen. Residential exposure to radon gas, for example, has similar cancer risks as passive smoking. Radiation is a more potent source of cancer when combined with other cancer-causing agents, such as radon plus tobacco smoke. Radiation can cause cancer in most parts of the body, in all animals and at any age. Children are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect. Medical use of ionizing radiation is a small but growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of medical imaging.

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.

Non-ionizing radio frequency radiation from mobile phones, electric power transmission and other similar sources has been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer. Evidence, however, has not supported a concern

e). Heredity.

The vast majority of cancers are non-hereditary (sporadic). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation that has a large effect on cancer risk and these cause less than 3–10% of cancer. Some of these syndromes include: certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer, and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which is present in about 3% of people with colorectal cancer, among others. Taller people have an increased risk of cancer because they have more cells than shorter people. Since height is genetically determined to a large extent, taller people have a heritable increase of cancer risk.

f). Physical agents.

Some substances cause cancer primarily through their physical, rather than chemical, effects. A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers that are a major cause of mesothelioma (cancer of the serous membrane) usually the serous membrane surrounding the lungs. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool and rock wool, are believed to have similar effects. Non-fibrous particulate materials that cause cancer include powdered metallic cobalt and nickel and crystalline silica (quartz, cristobalite and tridymite). Usually, physical carcinogens must get inside the body (such as through inhalation) and require years of exposure to produce cancer. Physical trauma resulting in cancer is relatively rare. Claims that breaking bones resulted in bone cancer, for example, have not been proven. Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer or brain cancer. One accepted source is frequent, long-term application of hot objects to the body. It is possible that repeated burns on the same part of the body, such as those produced by kanger and kairo heaters (charcoal hand warmers), may produce skin cancer, especially if carcinogenic chemicals are also present. Frequent consumption of scalding hot tea may produce esophageal cancer. Generally, it is believed that cancer arises, or a pre-existing cancer is encouraged, during the process of healing, rather than directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation. Chronic inflammation has been hypothesized to directly cause mutation. Inflammation can contribute to proliferation, survival, angiogenesis and migration of cancer cells by influencing the tumor microenvironment. Oncogenes build up an inflammatory pro-tumorigenic microenvironment.

g.Hormones.

Some hormones play a role in the development of cancer by promoting cell proliferation. Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis. Hormones are important agents in sex-related cancers, such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer.Other factors are relevant: obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer. Osteosarcoma may be promoted by growth hormones. Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.

h). Autoimmune diseases.

There is an association between celiac disease and an increased risk of all cancers. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis and strict treatment, probably due to the adoption of a gluten-free diet, which seems to have a protective role against development of malignancy in people with celiac disease. However, the delay in diagnosis and initiation of a gluten-free diet seems to increase the risk of malignancies. Rates of gastrointestinal cancers are increased in people with Crohn's disease and ulcerative colitis, due to chronic inflammation. Also, immunomodulators and biologic agents used to treat these diseases may promote developing extra-intestinal malignancies.

MOLECULAR BASIS OF CANCER.

Cancer is fundamentally a disease of tissue growth regulation. In order for a normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered. The affected genes are divided into two broad categories:

- Oncogenes are genes that promote cell growth and reproduction.

- Tumor suppressor genes are genes that inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in multiple genes are required to transform a normal cell into a cancer cell.

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, leading to the expression of viral oncogenes in the affected cell and its descendants.

Replication of the data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If a significant error occurs, the damaged cell can self-destruct through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation or hypoxia.[84]

The errors that cause cancer are self-amplifying and compounding, for example:

A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.

A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.

A further mutation may cause loss of a tumor suppressor gene, disrupting the apoptosis signaling pathway and immortalizing the cell.

A further mutation in the signaling machinery of the cell might send error-causing signals to nearby cells.

The transformation of a normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape more controls that limit normal tissue growth. This rebellion-like scenario is an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution, drives progression towards more invasive stages.[85] Clonal evolution leads to intra-tumour heterogeneity (cancer cells with heterogeneous mutations) that complicates designing effective treatment strategies.

Characteristic abilities developed by cancers are divided into categories, specifically evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential, metastasis, reprogramming of energy metabolism and evasion of immune destruction.[26][27]