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QUESTIONS

1. WHAT DO YOU UNDERSTAND BY PRIMARY AND SIMPLE OBESITY

**Obesity** is a medical condition in which excess body fat has accumulated to an extent that it may have a negative effect on health. **Obesity** is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility. Obesity is a multifactorial pathology that can be related to an altered nutritional behavior or secondary to genetic, hypothalamic, iatrogenic or endocrine disease. At the base of obesity is adiposopathy (or “sick fat”) defined as “pathologic adipose tissue anatomic/functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that result in adverse endocrine and immune responses that may cause or worsen metabolic disease”.Adiposopathy is sustained by adipocyte hypertrophy, visceral adiposity and ⁄or ectopic fat deposition and secretion of hormones, like leptin, and proinflammatory protein, like the plethora of cytokines, that in turn may lead to metabolic disease.Therefore, we can classified obesity as a primary disease since the adiposopathy determines the dysregulation of the metabolic pathways. Metabolic diseases most associated with primary obesity contribute to atherosclerosis, hypertension, dyslipidemia, diabetes type II, hyperandrogenemia in women and hypoandrogenemia/hyperestrogenemia in men.There may be pathogenic immune and adiposopathic endocrine responses for the cardiovascular system or other systems. Sometimes, adiposopathy may cause atherosclerotic risk factors such as type 2 diabetes mellitus or dyslipidemia.The diagnosis and treatment of obesity plays, therefore, an important role since this pathology is associated with an increased risk of numerous diseases and reduced life expectancy.

1. HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECT OBESITY

Lifestyle modification interventions including behavioral treatment, diet modification, and physical activity, are the cornerstones of primary and secondary prevention/treatment of pediatric obesity.Some studies have shown long-lived effects on pediatric overweightspecially from family-based or other behavioral treatment without adverse effects on growth and development. The metabolic syndrome is a condition characterized by a special constellation of reversible major risk factors for cardiovascular disease and type 2 diabetes. The main, diagnostic, components are reduced HDL-cholesterol, raised triglycerides, blood pressure and fasting plasma glucose, all of which are related to weight gain, specifically intra-abdominal/ectopic fat accumulation and a large waist circumference. Using internationally adopted arbitrary cut-off values for waist circumference, having metabolic syndrome doubles the risk of cardiovascular disease, but offers an effective treatment approach through weight management. Metabolic syndrome now affects 30–40% of people by age 65, driven mainly by adult weight gain, and by a genetic or epigenetic predisposition to intra-abdominal/ectopic fat accumulation related to poor intra-uterine growth. Metabolic syndrome is also promoted by a lack of subcutaneous adipose tissue, low skeletal muscle mass and anti-retroviral drugs. Reducing weight by 5–10%, by diet and exercise, with or without, anti-obesity drugs, substantially lowers all metabolic syndrome components, and risk of type 2 diabetes and cardiovascular disease. Other cardiovascular disease risk factors such as smoking should be corrected as a priority. Anti-diabetic agents which improve insulin resistance and reduce blood pressure, lipids and weight should be preferred for diabetic patients with metabolic syndrome. Bariatric surgery offers an alternative treatment for those with BMI ≥ 40 or 35–40 kg/m2 with other significant co-morbidity. The prevalence of the metabolic syndrome and cardiovascular disease is expected to rise along with the global obesity epidemic: greater emphasis should be given to effective early weight-management to reduce risk in pre-symptomatic individuals with large waists.

3) Outline the aetiology of cancer and its molecular basis

Cellular functions are controlled by proteins, and because these proteins are encoded by DNA organized into genes, **molecular** studies have shown that **cancer** is a paradigm of acquired genetic disease The etiology of cancer in children is multifactorial, involving both genetic and environmental factors; in neonates, predisposing [genetic factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity) frequently play an important role. An acquired or inherited abnormality of a cancer-predisposing gene that is critical during embryogenesis underlies many cases of neonatal cancer. [Malignant transformation](https://www.sciencedirect.com/topics/medicine-and-dentistry/malignant-transformation) of normal cells results from the activation or suppression of these cancer-predisposing genes. The [retinoblastoma](https://www.sciencedirect.com/topics/nursing-and-health-professions/retinoblastoma) gene at 13q is an example of a constitutional [chromosomal abnormality](https://www.sciencedirect.com/topics/medicine-and-dentistry/chromosome-aberration) that results in a high risk of malignancy.

A number of well-defined hereditary conditions are associated with an increased incidence of specific neoplasms; these are listed in Table 80-3. Except for retinoblastoma, [hepatoblastoma](https://www.sciencedirect.com/topics/medicine-and-dentistry/hepatoblastoma), and [Wilms’ tumor](https://www.sciencedirect.com/topics/medicine-and-dentistry/wilms-tumor), the neoplasms associated with these syndromes seldom manifest in the [neonatal period](https://www.sciencedirect.com/topics/medicine-and-dentistry/newborn-period), but the associated abnormalities may be recognized early, allowing for regular screening. Cancer is caused by changes (mutations) to the DNA within cells. The DNA inside a cell is packaged into a large number of individual genes, each of which contains a set of instructions telling the cell what functions to perform, as well as how to grow and divide. Errors in the instructions can cause the cell to stop its normal function and may allow a cell to become cancerous.

**What do gene mutations do?**

A gene mutation can instruct a healthy cell to:

* **Allow rapid growth.** A gene mutation can tell a cell to grow and divide more rapidly. This creates many new cells that all have that same mutation.
* **Fail to stop uncontrolled cell growth.** Normal cells know when to stop growing so that you have just the right number of each type of cell. Cancer cells lose the controls (tumor suppressor genes) that tell them when to stop growing. A mutation in a tumor suppressor gene allows cancer cells to continue growing and accumulating.
* **Make mistakes when repairing DNA errors.** DNA repair genes look for errors in a cell's DNA and make corrections. A mutation in a DNA repair gene may mean that other errors aren't corrected, leading cells to become cancerous.

These mutations are the most common ones found in cancer. But many other gene mutations can contribute to causing cancer.

**What causes gene mutations?**

Gene mutations can occur for several reasons, for instance:

* **Gene mutations you're born with.** You may be born with a genetic mutation that you inherited from your parents. This type of mutation accounts for a small percentage of cancers.
* **Gene mutations that occur after birth.** Most gene mutations occur after you're born and aren't inherited. A number of forces can cause gene mutations, such as smoking, radiation, viruses, cancer-causing chemicals (carcinogens), obesity, hormones, chronic inflammation and a lack of exercise.

Gene mutations occur frequently during normal cell growth. However, cells contain a mechanism that recognizes when a mistake occurs and repairs the mistake. Occasionally, a mistake is missed. This could cause a cell to become cancerous.

MOLECULAR BASIS

Generation time is the time required for a cell to complete a cycle in cell division (see figure [The cell cycle](https://www.merckmanuals.com/professional/hematology-and-oncology/overview-of-cancer/cellular-and-molecular-basis-of-cancer#v39241519)) and give rise to 2 daughter cells. Malignant cells, particularly those arising from the bone marrow or lymphatic system, may have a short generation time, and there usually are a smaller percentage of cells in G0 (resting phase). Initial exponential tumor growth is followed by a plateau phase when cell death nearly equals the rate of formation of daughter cells. The slowing in growth rate may be related to exhaustion of the supply of nutrients and oxygen for the rapidly expanding tumor. Small tumors have a greater percentage of actively dividing cells than do large tumors.

A subpopulation within many tumors, identified by surface proteins, may have the properties of primitive "normal" stem cells, as found in the early embryo. Thus, these cells are capable of entering a proliferative state. They are less susceptible to injury by drugs or irradiation. They are believed to repopulate tumors after surgical, chemical, or radiation treatment. As a tumor grows, nutrients are provided by direct diffusion from the circulation. Local growth is facilitated by enzymes (eg, proteases) that destroy adjacent tissues. As tumor volume increases, tumor angiogenesis factors, such as vascular endothelial growth factor (VEGF), are produced by tumors to promote formation of the vascular supply required for further tumor growth.

Almost from inception, a tumor may shed cells into the circulation. From animal models, it is estimated that a 1-cm tumor sheds > 1 million cells/24 h into the venous circulation. Circulating tumor cells are present in many patients with advanced cancer and even in some with localized disease. Although most circulating tumor cells die in the intravascular space, an occasional cell may adhere to the vascular endothelium and penetrate into surrounding tissues, generating independent tumors (metastases) at distant sites. Metastatic tumors grow in much the same manner as primary tumors and may subsequently give rise to other metastases. Genetic mutations are responsible for the generation of cancer cells and are thus present in all cancers. These mutations alter the quantity or function of protein products that regulate cell growth and division and DNA repair. Two major categories of mutated genes are

* Oncogenes
* Tumor suppressor genes

**Oncogenes**

Oncogenes are abnormal forms of normal genes (proto-oncogenes) that regulate various aspects of cell growth and differentiation. Mutation of these genes may result in direct and continuous stimulation of the pathways (eg, cell surface growth factor receptors, intracellular signal transduction pathways, transcription factors, secreted growth factors) that control cellular growth and division, cellular metabolism, DNA repair, angiogenesis, and other physiologic processes.

There are > 100 known oncogenes that may contribute to human neoplastic transformation. For example, the *RAS* gene encodes the ras protein, which carries signals from membrane-bound receptors down the RAS-MAPKinase pathway to the cell nucleus, and thereby regulates cell division. Mutations may result in the inappropriate activation of the ras protein, leading to uncontrolled cell growth. The ras protein is abnormal in about 25% of human cancers.