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ASSIGNMENT 2

1. What do you understand by Primary Obesity?

   Primary obesity is a type of obesity caused mainly by increased food intake and decreased energy usage.

2. How does drug therapy and congenital syndrome affect Secondary Obesity?

   Congenital Syndrome
   Secondary obesity is a characteristic feature of many congenital and genetic disorders, such as AHO, Alstrom–Hallgren syndrome, Bar- det–Biedl syndrome, Beckwith–Wiedeman syn- drome, Carpenter syndrome, Cohen syndrome and Prader–Willi syndrome (PWS), the latter being one of the most common syndromic forms of obesity in children. In addition to being overweight, children with genetic syndromes associated with obesity typically have characteristic physical findings, including dysmorphic features, developmental delay and mental retardation.

   Drug Therapy
   Drug-induced obesity is a serious side effect of many commonly used drugs leading to noncompliance with therapy and to exacerbation of comorbid conditions related to obesity. Improved glycemic control achieved by insulin, insulin secretagogues or thiazolidinedione therapy is generally accompanied by obesity. It is a problematic side effect of therapy due to the known deleterious effect of obesity on glucose control, increased blood pressure and worsening lipid profile. Obesity may be lessened or prevented by adherence to diet and exercise or combination therapy with metformin. Obesity is also common in psychotropic therapy. The atypical antipsychotic drugs (clozapine, olanzepine, risperidone and quetiapine) are known to cause marked obesity. Antidepressants such as amitriptyline, mirtazapine and some serotonin reuptake inhibitors (SSRIs) also may promote appreciable obesity that cannot be explained solely by improvement in depressive symptoms. The same phenomenon is observed with mood stabilizers such as lithium, valproic acid and carbamazepine. Antiepileptic drugs (AEDs) that promote obesity include valproate, carbamazepine and gabapentin. Lamotrigine is an AED that is weight-neutral, while topiramate and zonisamide may induce weight loss.

3. Discuss the etiology of cancer and its molecular basis.

Etiology of Cancer

All cancers are multifactorial in origin. They include genetic, hormonal, metabolic, physical, chemical and environmental factors. Most human cancers are spontaneous. All cancers originate usually from one aberrant cell, which goes on to multiply and produce a tumor mass. One mutation occurs out of 10^6 cell divisions. By the time a person reaches adulthood, about 10^{26} cell divisions have occurred. Thanks to the surveillance by the immune system, these aberrant cells are usually destroyed. As age advances, the number of mutations accumulate, hence the statistical probability of the incidence of cancer is increased. No wonder, cancer is a disease of old age, especially after 60 years.

Molecular Basis of Cancer

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 (e.g., 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-MAP Kinase 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. Other oncogenes have been implicated in specific cancers. These include:

- *HER2* (amplified in breast and gastric cancer and less commonly in lung cancer)
- *BCRABL1* (a translocation of 2 genes that underlies chronic myeloid leukemia and some B-cell acute lymphocytic leukemias)
- *CMYC* (Burkitt lymphoma)
- *NMYC* (small cell lung cancer, neuroblastoma)
- *EGFR* (adenocarcinoma of the lung)
- *EML4ALK* (a translocation that activates the ALK tyrosine kinase and causes a unique form of adenocarcinoma of the lung)

Specific oncogenes may have important implications for diagnosis, therapy, and prognosis (see individual discussions under the specific cancer type).

Oncogenes typically result from:

- Acquired somatic cell point mutations (e.g., due to chemical carcinogens)
- Gene amplification (e.g., an increase in the number of copies of a normal gene).
- Translocations (in which pieces of different genes merge to form a unique sequence).

These changes may either increase the activity of the gene product (protein) or change its function. Occasionally, mutation of genes in germ cells results in inheritance of a cancer predisposition.

Tumor suppressor genes

Genes such as *TP53*, *BRCA1*, and *BRCA2* play a role in normal cell division and DNA repair and are critical for detecting inappropriate growth signals or DNA damage in cells. If these genes, as a result of inherited or acquired mutations, become unable to function, the system for monitoring DNA integration becomes inefficient, cells with spontaneous genetic mutations persist and proliferate, and tumors result.
As with most genes, 2 alleles are present that encode for each tumor suppressor gene. A defective copy of one gene may be inherited, leaving only one functional allele for the individual tumor suppressor gene. If a mutation is *acquired* in the functional allele, the normal protective mechanism of the 2nd normal tumor suppressor gene is lost.
The important regulatory protein, p53, prevents replication of damaged DNA in normal cells and promotes cell death (apoptosis) in cells with abnormal DNA. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. *TP53*mutations are passed to daughter cells, conferring a high probability of replicating error-prone DNA, and neoplastic transformation results. *TP53* is defective in many human cancers.
BRCA1 and *BRCA2* mutations that decrease function increase risk of breast and ovarian cancer.
Another example, the retinoblastoma (*RB*) gene encodes for the protein Rb, which regulates the cell cycle by stopping DNA replication. Mutations in the *RB* gene family occur in many human cancers, allowing affected cells to divide continuously.
As with oncogenes, mutation of tumor suppressor genes such as *TP53* or *RB* in germ cell lines may result in vertical transmission and a higher incidence of cancer in offspring.

Chromosomal abnormalities

Chromosomal abnormalities can occur through deletion, translocation, or duplication. If these alterations activate or inactivate genes that result in a proliferative advantage over normal cells, then a cancer may develop.
Chromosomal abnormalities occur in most human cancers. In some congenital diseases (Bloom syndrome, Fanconi anemia, Down syndrome), DNA repair processes are defective and chromosome breaks are frequent, putting children at high risk of developing acute leukemia and lymphomas.

Other influences

Most epithelial cancers likely result from a sequence of mutations that lead to neoplastic conversion. For example, the development of colon cancer in familial polyposis takes place through a sequence of genetic events: epithelium hyperproliferation (loss of a suppressor gene on chromosome 5), early adenoma (change in DNA methylation), intermediate adenoma (overactivity of the *RAS* oncogene), late adenoma (loss of a suppressor gene on chromosome 18), and finally, cancer (loss of a gene on chromosome 17). Further genetic changes may be required for metastasis.

Telomeres are nucleoprotein complexes that cap the ends of chromosomes and maintain their integrity. In normal tissue, telomere shortening (which occurs with aging) results in a finite limit in cell division. The enzyme telomerase, if activated in tumor cells, provides for new telomere synthesis and allows continuous proliferation of cancers.