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BCH ASSIGNEMNT

1. WHAT DO YOU UNDERSTAND BY PRIMARY OR SIMPLE OBESITY

Primary exogenous obesity has been defined as the intake of more food than a person's activity level warrants, leading to excess adipose tissue in the body. Obesity increases the likelihood of various diseases and conditions, particular cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, osteoarthritis, and depression. As a result, obesity has been found to reduce life expectancy.

Obesity is a medical condition in which excess body fat has accumulated to an extent that it may have a negative effect on health. A certain amount of body fat is necessary for storing energy, heat insulation, shock absorption, and other functions. It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist-hip ratio and total cardiovascular risk factors. BMI is closely related to both percentage body fat and total body fat. BMI is defined as the subject's weight divided by the square of their height and is calculated as follows.

$$B=M/H^2$$

where *m* and *h* are the subject's weight and height respectively. BMI is usually expressed in kilograms of weight per metre squared of height.

Any BMI ≥ 35 or 40 kg/m2 is *severe obesity*.

- A BMI of ≥ 35 kg/m2 and experiencing obesity-related health conditions or ≥40–44.9 kg/m2 is *morbid obesity*.
- A BMI of ≥ 45 or 50 kg/m2 is *super obesity*.

2. HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECTS OBESITY

Effect of drug therapy/medication on obesity:

Medication treatment of obesity should be used only in patients who have health risks related to obesity. Medications should be used in patients with a BMI greater than 30 or in those with a BMI of greater than 27 who have other medical conditions (such as high blood pressure, diabetes, high blood cholesterol) that put them at risk for developing heart disease. Medications should not be used for cosmetic reasons. Medications should only be used as an adjunct to diet modifications and an exercise program.

Like diet and exercise, the goal of medication treatment has to be realistic. With successful medication treatment, one can expect an initial weight loss of at least 5 pounds during the first month of treatment, and a total weight loss of 10%-15% of the initial body weight. It is also important to remember that these medications only work when they are taken. When they are discontinued, weight gain often occurs.

The first class (category) of medication used for weight control cause symptoms that mimic the sympathetic nervous system. They cause the body to feel "under stress" or "nervous." As a result, the major side effect of this class of medication is high blood pressure. This class of medication includes sibutramine and phentermine. These medications also decrease appetite and create a sensation of fullness. Hunger and fullness (satiety) are regulated by brain chemicals called neurotransmitters. Examples of neurotransmitters include serotonin, norepinephrine, and dopamine. Anti-obesity medications that suppress appetite do so by increasing the level of these neurotransmitters at the junction (called synapse) between nerve endings in the brain.

Effect of congenital syndrome:

The syndromic forms of obesity are often associated with phenotypes in addition to the early-onset severe obesity. This may be caused by change in a single gene or a larger chromosomal region encompassing several genes. Obesity is a feature of almost 100 syndromes; a little over half are not yet named, and 13.9% have more than one name. The co-presenting phenotypes often include intellectual disability, dysmorphic facies, or organ-system specific abnormalities. The most frequent forms of syndromic obesity are Bardet Biedl and Prader Willi syndrome.

Bardet- biedel syndrome (BBS):

BBS is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties and hypogonadism The phenotype evolves slowly through the first decade of life, and often the only manifestation seen at birth may be post-axial polydactyly, with or without other limb abnormalities. Gradual onset of night blindness, along with photophobia and the loss of central and/or color vision is the next definitive finding, often leading to the diagnosis. Obesity is present in the vast majority (72–86%) of the individuals, although the birth weight may be normal. There is a high prevalence of Type 2 diabetes, hypogonadism, cognitive deficit, labile behavior, speech deficit, renal and cardiac anomalies The biological defect for the syndrome is an abnormality in immotile cilia that primarily function as the sensory organelle regulating signal transduction pathways. The functional unit of the immotile cilia, or the BBSome, comprises of the cilium, the basal body, the chaperonin complex and other membrane proteins that maintain the function of the cilium. At the time of this writing, mutations in 16 different genes that alter the function of the BBSome at various levels have been identified (BBS1–BBS16).

Prader Willi syndrome (PWS):

PWS is the commonest cause of syndromic obesity around the world (1 in 15,000–25,000 births).It is characterized by severe neonatal hypotonia, eating disorders evolving in several phases (from anorexia and failure to thrive in the early infancy to severe hypephagia with food compulsivity by about 4–8 years of age). Additional features include dysmorphic facies, global cognitive impairment, behavioral abnormalities, hypotonia, delayed motor development and hormonal deficiencies such as growth hormone, hypothyroidism, hypogonadism and ghrelin abnormalities. The genetic defect in PWS is the inactivation of the Prader-Willi critical region (PWCR) located on the 15q11-13 region of the paternal chromosome. The PWCR on the maternal chromosome is imprinted, and therefore epigenetically silenced through methylation, leading to mono-allelic expression of the paternal genes. Majority of cases of PWS are caused by interstitial deletions of the paternal region of the PWCR (65–70%), while others by maternal uniparental disomy (20–30%) and mutations within the imprinting center (2–5%). At least 5 genes, located in the PWCR and expressed in hypothalamus, have been implicated without clarity of their roles. A recent study of pluripotent stem cells derived neurons from individuals with microdeletion in the PWCR indicates a lower expression

of proconvertase 1 (PC1), previously implicated in monogenic obesity, potentially offering a unifying explanation for the phenotype

3. OUTLINE THE AETIOLOGY OF CANCER AND ITS MOLECULAR BASIS.

Causes/etiology of cancer:

- Mutations in Genes That Regulate Apoptosis Allow Cancer Cells to Escape Suicide: To achieve net cell proliferation, it is necessary not only to drive cells into division, but also to keep cells from committing suicide by apoptosis. There are many normal situations in which cells proliferate continuously, but the cell division is exactly balanced by cell loss. In the germinal centers of lymph nodes, for example, B cells proliferate rapidly but most of their progeny are eliminated by apoptosis. Apoptosis is thus essential in maintaining the normal balance of cell births and deaths in tissues that undergo cell turnover.

- Mutations in the *p53* Gene Allow Cancer Cells to Survive and Proliferate despite DNA Damage: The *p53 gene*-named for the molecular mass of its protein product-may be the most important gene in human cancer. This tumor suppressor gene is mutated in about half of all human cancers. What makes *p53* so critical? The answer lies in its triple involvement in cell-cycle control, in apoptosis, and in maintenance of genetic stability-all aspects of the fundamental role of the p53 protein in protecting the organism against cellular damage and disorder.

- DNA Tumor Viruses Activate the Cell's Replication Machinery by Blocking the Action of Key Tumor Suppressor Genes: DNA tumor viruses cause cancer mainly by interfering with cell-cycle controls, including those that depend on p53. To understand this type of viral carcinogenesis, it is important to understand the life history of the virus. Viruses use the DNA replication machinery of the host cell to replicate their own genomes. To make many infectious virus particles from a single host cell, a DNA virus has to commandeer this machinery and drive it hard, breaking through the normal constraints on DNA replication and usually killing the host cell in the

process. Typically, however, the virus also has another option: it can propagate its genome as a quiet, well-behaved passenger in the host cell, replicating in parallel with the host cell's DNA in the course of ordinary cell division cycles. The virus can switch between these two modes of existence, remaining latent and harmless or proliferating to generate infectious particles according to circumstances. No matter which way of life the virus is following, it is not in its interests to cause cancer. But genetic accidents can occur, such that the virus misuses its equipment for commandeering the DNA replication machinery, and instead of switching on rapid replication of its own genome, switches on persistent proliferation of the host cell.

- Telomere Shortening May Pave the Way to Cancer in Humans: As we saw earlier, most human cells seem to have a built-in limit to their proliferation: they show replicative senescence, at least when grown in culture. Replicative cell senescence in humans is thought to be caused by changes in the structure of telomeres-the repetitive DNA sequences and associated proteins that cap the ends of each chromosome. These telomeric DNA sequences are synthesized and maintained by a special mechanism that requires the enzyme telomerase.

- Defects in DNA mismatch repair provide an alternative route to colorectal cancer: there is a second, and actually commoner, kind of hereditary predisposition to colon carcinoma in which the course of events is quite different from the one we have described for FAP. In patients with this condition, called hereditary nonpolyposis colorectal *cancer,* or *HNPCC,* the probability of colon cancer is increased without any increase in the number of colorectal polyps (adenomas). Moreover, the cancer cells in the tumors that develop are unusual, inasmuch as examination of their chromosomes in a microscope reveals a normal (or almost normal) karyotype and a normal (or almost normal) number of chromosomes.

<u>Molecular basis of cancer:</u>

Studies of developing embryos and transgenic mice have helped to reveal the functions of many cancer-critical genes. Most of the genes found to

be mutated in cancer, both oncogenes and tumor suppressor genes, code for components of the pathways that regulate the social and proliferative behavior of cells in the body—in particular, the mechanisms by which signals from a cell's neighbors can impel it to divide, differentiate, or die. Other cancer-critical genes are involved in maintaining the integrity of the genome and guarding against damage. The molecular changes that allow cancers to metastasize, however, escaping the parent tumor and growing in foreign tissues, are still largely unknown.

DNA viruses such as papillomaviruses can promote the development of cancer by sequestering the products of tumor suppressor genes in particular, the Rb protein, which regulates cell division, and the p53 protein, which is thought to act as an emergency brake on cell division in cells that have suffered genetic damage and to call a halt to cell division in senescent cells with shortened telomeres.

The p53 protein has a dual role, regulating both progression through the cell cycle and the initiation of apoptosis. So loss or inactivation of p53, which occurs in about half of all human cancers, is doubly dangerous: it allows genetically damaged and senescent cells to continue to replicate their DNA, increasing the damage, and it allows them to escape apoptosis. The loss of p53 function may contribute to the genetic instability of many full-blown metastasizing cancers.

Generally speaking, the steps of tumor progression can be correlated with mutations that activate specific oncogenes and inactivate specific tumor suppressor genes. But different combinations of mutations are found in different forms of cancer and even in patients that nominally have the same form of the disease, reflecting the random way in which mutations occur. Nevertheless, many of the same types of genetic lesions are encountered repeatedly, suggesting that there is only a limited number of ways in which our defenses against cancer can be breached.