NAME: SOJI-OYE IREOLUWA FAITH

MATRIC NO: 17/ MHS05/019

DEPARTMENT: MEDICINE AND SURGERY

COURSE TITLE: MEDICAL BIOCHEMISTRY IV

COURSE CODE: BCH 313

**ASSIGNMENT**

1. WHAT DO YOU UNDERSTAND BY PRIMARY OR SIMPLE OBESITY

2. HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECTS OBESITY

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

1. Primary exogenous obesity is defined as a state of excess adipose tissues in the body. This condition occurs in 5%- 30% of the adult population. It is not associated with clinical condition and is classified based on nutrition (based on imbalance between food intake and energy expenditure).

2a. **CONGENITAL SYNDROME AFFECTING OBESITY**: Constitutional obesity and mental retardation cooccur in several multiple congenital anomaly syndromes, including Prader–Willi syndrome, Bardet–Biedl syndrome, Cohen syndrome, Albright hereditary osteodystrophy, and Borjeson–Forssman–Lehmann syndrome as well as some rarer disorders. Although hypothalamic–pituitary axis abnormalities are thought to be a possible causative mechanism in some of these disorders, current knowledge is insufficient to explain the pathophysiologic mechanism of obesity in most multiple congenital anomaly/mental retardation syndromes. The chromosomal location of many of these syndromes is known, and studies are ongoing to identify the causative genes. Further delineation of the functions of the underlying genes will likely be instructive regarding mechanisms of appetite, satiety, and obesity in the general population.

Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic condition due to paternal loss of imprinted genes on chromosome 15 and characterized by a range of mental and physical findings including obesity that can be life-threatening. The **obesity** associated with PWS results from a chronic imbalance between energy intake and expenditure due to hyperphagia, decreased physical activity, reduced metabolic rate and an inability to vomit. Individuals with PWS have a lower lean body mass compared with controls contributing to reduced energy expenditure.

Bardet-Biedl syndrome (BBS) is a genetic disorder with obesity as one of the major phenotypic criterion, which is proposed to be of neuroendocrine origin. Therefore, disturbances in appetite-regulating hormones have been considered as causative factors.

Cohen syndrome is a rare autosomal recessive disorder resulting from mutations of a gene. The syndrome expresses as truncal obesity, hypotonia, psychomotor deficiencies, ocular abnormalities, and characteristic facial features.

Borjeson-Forssman-Lehmann syndrome. Borjeson-Forssman-Lehmann syndrome (BFLS) is a rare X-linked obesity syndrome characterized by intellectual deficit, truncal obesity, characteristic facial features, hypogonadism, tapered fingers and short toes.

Carpenter syndrome besides obesity, includes mental retardation, short stature,

brachicephalus, polydactyly, foot syndactyly, cryptorchidism, hypogonadism in boys, umbilical hernias and high palate.

Albright’s hereditary osteodistrophy involves a phenotype with short stature and

obesity, along with a shortening of the 4th metacarpal bone as well as pseudohypoparathyroidism type 1a (PHP 1a) and pseudopseudohypoparathyroidism (PPHP).

2b. **DRUG THERAPY AFFECTING OBESITY:** In the obese, modifications in body constitution (higher percentage of fat and lower percentage of lean tissue and water) can affect drug distribution in the tissues. For slightly liposoluble molecules (e.g., digoxin, antipyrine), the equilibrium distribution volume (V), total and per kilogram weight, is significantly less than that of control subjects. With lipophilic drugs (e.g., barbiturates, benzodiazepines), this parameter is significantly increased, explaining the prolongation of the plasma elimination half-life. For drugs that are almost equally soluble in water and oil (methyl xanthines, aminoglycosides), the volume is slightly increased in the obese. The other main factors involved in drug diffusion in the tissues are binding to plasma and tissue proteins, and regional blood flow. In the obese the binding of drugs to albumin does not seem to be altered. In most publications concerning drugs with biotransformation as the principal elimination route, the total plasma clearance is not reduced. Up to the present, there are no reports of any impairment involving renal elimination of drugs in the obese. Dose-adjustment of hydrophilic drugs is assessed according to the ideal weight of the individual obese subject; with lipophilic drugs the loading dose can be fixed according to the total weight; calculation of the maintenance dose depends on possible changes in the total clearance.

1. **AETIOLOGY OF CANCER AND ITS MOLECULAR BASIS**

The term cancer applies to a group of diseases in which cells grow abnormally. It may be defined as ***“malignant*** ***neoplasm.”*** Neoplasm means new growth. Neoplasiais a general term given to diseases that cause abnormal growth of cells.A mass of tissue formed as a result of abnormal excessive, uncoordinated, autonomous and purposeless proliferation of cells is called ***tumor*.** The branch of science dealing with the study of neoplasm or tumor is called oncology (oncos = tumor, logos = study). Tumors may be ‘benign’ (that is, it does not invade or spread to distant sites in the body and does not destroy the tissue in which it originates, i.e. a non-cancerous tumor) or “malignant” (that is, it invades and destroys the tissuein which it originates and can spread to other sites in the body via the blood stream and lymphatic systems).The term used for all malignant tumors is ***cancer*.**

**CARCINIGENESIS AND CARCINIGENS**

Carcinogenesis means formation of cancer. Agents which can induce cancer are called ***carcinogens.*** Carcinogens are a variety of external agents which are

divided into three groups:

* Chemical carcinogens
* Physical carcinogens
* Biologic carcinogens.

**Chemical Carcinogens:** Depending upon the mode of action of carcinogenic

chemicals, they are divided into two groups:

* ***Initiators*** of carcinogenesis
* ***Promoters*** of carcinogenesis.

**Initiators of carcinogenesis:** These are the chemical carcinogens which can initiatethe process of abnormal new growth of cells. These arefurther classified into two subgroups:

* ***Indirect*** acting carcinogens
* ***Direct*** acting carcinogens.

***Indirect acting carcinogens (Procarcinogens):*** Indirect acting carcinogens require prior metabolismto become carcinogenic. One or more enzyme catalyzedreactions convert procarcinogens to activecarcinogens. This is called metabolic activation of

procarcinogens. Examples of procarcinogens are:

• **Aromatic hydrocarbons,** e.g. Benzo [a] pyrene, Tobacco smoke, industrial and atmospheric pollutants.

• **Aromatic amines,** e.g. Benzidine, -naphthylamine, azo dyes used in rubber industries.

• **Naturally occurring products,** e.g. Aflatoxin B1.

• **Inorganic compounds,** e.g. Vinyl chloride, Asbestos, metals like nickel, lead, chromium, etc.

• **Nitrosamine compounds,** e.g. Dimethylnitrosamine, diethylnitrosamine found in whisky, new car interiors, tobacco smoke.

***Direct acting carcinogens:*** These do not require metabolic activation. These

include mainly various anticancer drugs, e.g. cyclophosphamide, nitrosourea, acetyl imidazole, etc.

**Promoters of carcinogenesis** Certain chemical substances are not carcinogenic butthey help the initiated cell to proliferate further arecalled promoters of carcinogenesis**.** Forexample, phenols, phenobarbital, artificial sweetnerslike saccharine and cyclamates.

**Action of Chemical Carcinogens**

Direct or indirect acting carcinogens are usually **electrophiles,** i.e. they are deficient in electrons (free radicals). These free radical carcinogens can covalently

bind to purines, pyrimidines and phosphodiester bonds of DNA causing unrepairable damage. These unrepaired damage generate mutations in DNA and mutation in DNA may lead to cancer.

**Physical Carcinogens:** Physical carcinogenic agent is radiant energy both

ultraviolet light and ionizing radiation, i.e. X-rays, α, β and γ-rays.These rays damage DNA which is the basic mechanism of carcinogenicity with radiant

energy. The main source of UV radiation is the sunlight, others are UV lamps, welder’s arcs etc. In humans, excessive exposure of UV rays can cause various

forms of skin cancers. Ionizing radiation of all kinds like X-rays, α, β and γ-rays, radioactive isotopes, protons, and neutrons can cause cancer.

***Mode of action of radiation***

• Ultraviolet light and ionizing radiation differ in their mode of action.

• UV rays damage the DNA by formation of **pyrimidine dimmers** in DNA or by formation of **apurinic** or **apyrimidine** sites in DNA.

• While ionizing radiations cause the formation of highly reactive **free radicals,** that can interact with DNA leading to molecular damage.

**Biologic Carcinogens**

• Biologic carcinogens are chiefly ***viruses, parasites*** and ***bacteria.*** The role of viruses in the causation ofcancer is more significant.

• Oncogenic (carcinogenic) viruses contain either DNA or RNA as their genome. The two types of carcinogenic viruses are:

* DNA oncogenic viruses
* RNA oncogenic viruses.

*DNA oncogenic viruses*

DNA oncogenic viruses are classified into five subgroups.

These are:

a. Papoviruses

b. Herpes viruses

c. Adenoviruses

d. Pox viruses

e. Hepadna viruses.

*RNA oncogenic viruses*

The RNA viruses use RNA as the genome. RNA

oncogenic viruses are **retroviruses** they contain the

enzyme ***reverse transcriptase***. All retroviruses are not

oncogenic. The examples of RNA oncogenic viruses are:

• Rous Sarcoma virus

• Leukemia sarcoma virus

• Mouse mammary tumor virus etc.

****

**Mechanism of viral carcinogenesis**

DNA and RNA oncogenic viruses differ in their mode of action.

***Mode of action of DNA oncogenic virus***

The DNA virus infects the host cell. Then, DNA virusbinds tightly to host cell DNA and causes alterations in gene expression of host cell DNA and thus causes

cancer by altering the types of protein made in cell. Viral oncoproteins bind to tumor supressors and inactivate them.

***Mode of action of RNA oncogenic virus***

The RNA viruses use RNA as the genome. The RNA gets copied by **reverse transcriptase** to produce single strand of viral DNA. Single strand of viral DNA is then copied to form another strand of complementary DNA, resulting in double stranded ***viral DNA*** or ***provirus***. The provirus is then integrated into the DNA of the host cell genome and may transform the cell into cancer cell.

**PROTO-ONCOGENES AND ONCOGENES**

Proto-oncogenes are normal genes which stimulatecell division. Cellular proto-oncogenes code for a number of proteins, e.g. growth factors, receptors, transcription factors and other proteins involved in cell proliferation. *When proto-oncogenes get mutated they become* **oncogenes.**

Oncogenes are genes capable of causing cancer. In the cancer cell, their normal proto-oncogenes are permanently changed to oncogenes and the balance between factors stimulating and the factors inhibiting cell growth is permanently lost resulting in increased proliferation.When oncogenes are expressed, they produce

mutated protiens, e.g. growth factors, receptors, transcription factors and other proteins involved in cell proliferation. Thus, various factors that cause cancer may all act through their effects on proto-oncogene. Radiation, chemical carcinogens and viruses may cause mutations in the proto-oncogene.