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COURSE TITLE: CELLULAR BIOCHEMISTRY.

ASSIGNMENT.

QUESTION.

1. What do you understand by primary obesity.
2. How does drug therapy and congenital syndrome affect secondary obesity.
3. Discuss the aetiology of cancer and its molecular basis.

ANSWERS.

1. Primary obesity is a multifactorial pathology that can be related to an altered nutritional behavior or in which excess body fat has accumulated to the extent that it may have an adverse effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m^2; the range 25–30 kg/m^2 is defined as overweight. Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility
2. Secondary obesity means that you have a medical condition that has caused you to gain weight. These diseases include endocrine disorders, hypothalamic disorders and some congenital conditions.

How Drug Therapy affect Secondary Obesity:

Sometimes it is not the drug itself causing weight gain; however, it is the side-effects from the drug. Some drugs stimulate arcuate nucleus of the hypothalamus causing a large appetite, and as a result, more food is been consumed. Others may affect how your body absorbs and stores glucose, which can lead to fat deposits in the midsection of your body. Drug-induced weight gain 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 weight gain. It is a problematic side effect of therapy due to the known deleterious effect of weight gain on glucose control, increased blood pressure and worsening lipid profile.

The atypical antipsychotic drugs (clozapine, olanzepine, risperidone and quetiapine) are known to cause marked weight gain. Antidepressants such as amitriptyline, mirtazapine and some serotonin reuptake inhibitors (SSRIs) also may promote appreciable weight gain 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.

How congenital syndrome affects Secondary Obesity:

Some of the most common endocrine disorders that can contribute to secondary disorder include:

- ✓ A deficiency in thyroid hormone (hypothyroidism) and
- ✓ Polycystic ovarian syndrome (PCOS).

There are also some rare causes of secondary obesity like Cushing's disease (hypercortisolism), hypothalamic injury like damage to the hypothalamus or disorders, and genetic mutations.

- ✓ **Hyperthyroidism:**

When your thyroid makes less of its hormones - as it does in hypothyroidism - your metabolism slows down. The more severe your hypothyroidism is, the more weight you'll gain. Some of the weight gain is fat, which may lead to obesity along the line but much of it is fluid buildup from the effects of an underactive thyroid on your kidney function.

- ✓ **Polycystic ovarian syndrome:**

PCOS can cause missed or irregular menstrual periods, excess hair growth, acne, infertility, and weight gain. Women with PCOS may be at higher risk for type 2 diabetes, high blood pressure, heart problems, and endometrial cancer.

3. **AETIOLOGY OF CANCER.**

Cancer is multifactorial in origin with complex mechanism of development. Studies showed that people of 45 years and above have a higher risk to developing the disease than others. Some risk factors that increase the likelihood of developing cancer are provided through epidemiological studies of human population.

Some of these risk factors are mentioned hereby:

- **Carcinogens**

1. Tobacco smoke; e.g. cigars, pipes, smokeless tobacco e.t.c.
2. Diet; e.g. saturated fats, high salt intake, alcohol, refined foods and sugar etc.
3. Pathogens; e.g. human papillomavirus (HPV), hepatitis B&C virus, HIV etc.

4. Radiation; e.g. ultraviolet radiation, X rays, radon gas, therapeutic radiology etc.

5. Environmental and Occupational Chemicals; e.g. air, water, and soil pollutants, lead, benzene, arsenic, mercury, cadmium, asbestos, vinyl chloride, polychlorinated biphenyl(PCB), dichlorodiphenyltrichloroethane(DDT) etc.

- **Steroid hormones**

Steroid hormones; e.g. oestrogen, testosterone,hormone replacement therapy etc.

- **Population demographics**

Population demographics; e.g. age, race, sex and economy.

- **Hereditary factors**

Hereditary factors; e.g. inherited mutated breast cancer anti-tumour (BRCA1 or BRCA2) and DNA repairing (MSH2, MLH1 etc.) genes. An inherited gene mutation is the one that is present in the germ cells which formed the foetus and thus can be passed from one generation to the next compare to somatic or sporadic mutation which is not present in the germ cells and thus not transmitted to next generation. About 70 genes of the cancer genes are associated with hereditary mutations while 342 of the cancer genes are associated with somatic mutations. When one has Inherited an abnormal copy of a gene, the risk of the person developing a cancer increases and makes the inherited cancer tending to occur earlier in life than cancers of the same type that are not inherited. For example, BRCA1 and BRCA2 are human genes that produce anti-tumour proteins which help repair damaged DNA and thus ensuring the stability of the cell's genetic material. When either of these genes is mutated such that its protein product is not made or malfunctioned, DNA damage may not be repaired properly thereby causing additional genetic alterations that can lead to cancer. BRCA1 and BRCA2 mutations account for about 20 to 25 per cent of hereditary breast cancers, about 5 to 10 per cent of all breast cancers and around 15 per cent of ovarian cancers. Breast cancers associated with inherited mutated BRCA1 and BRCA2 tend to develop at younger ages than sporadic breast cancers. A harmful BRCA1 or BRCA2 mutation can be inherited from a person's mother or father. Each child of a parent who carries a mutation in one of these genes has a 50 per cent chance of inheriting the mutation. The effects of mutations in BRCA1 and BRCA2 are seen even when a person's second copy of the gene is normal. Carcinogens are biological, chemical, or physical agents that cause damage to a cell that leads to cancer. Carcinogens cause the greatest risk factors for cancer and on prolong exposure they induce mutation in a cell which may finally lead to the development of cancers. They cause damage to DNA of the cell either by covalently binding to Purines, pyrimidines and phosphodiester bonds of DNA, formation of pyrimidine dimers in DNA, production of free radicals or insertion into the host genome of viral oncogene. A large number of carcinogens accompanying food and beverages to enter the body. Obesity, according to World Health Organization (WHO), which is pandemic, increases the risk for such cancers as oesophagus, colorectal, breast, endometrium and kidney. From a prospective cancer prevention cohort, 14% of cancer deaths in men and that of 20% in women are attributed to overweight and obesity. overweight and obesity were reported to increase the risk of death for prostrate, breast, cervix, uterus, ovary, oesophagus, colorectal, liver, gall bladder, pancreas, kidneys and stomach cancers perhaps due to higher circulating level of oestrogen, insulin and other hormones that accompany increased body fat. Refined sugar, such sugar-concentrated foods as honey, evaporated cane juice etc., and refined flour products, have high energy but low nutrients, do result in diabetes. Diabetes in multiple studies showed a high risk factor for colorectal, endometrial and pancreatic cancers. Foods such as diary product, eggs, and meat that have no fibre or low fibre such as refined grain product were also found to increase the risk of rectal cancer. In a meta-analysis study, it was found that excessive consumption of red meat and processed red meat high in saturated fat significantly increased the risk of

colorectal and breast cancers perhaps due to the formation of heterocyclic amines and polycyclic aromatic hydrocarbons on cooking meat at high temperature. Furthermore, affirmed high alcohol consumption predisposition in the development of mouth throat, liver and probably of breast, colon and rectum cancers thereby given the worldwide incidence and mortality rates of cancer cases due to alcohol consumption as 3.6% and 3.5% respectively.

MOLECULAR BASIS OF CANCER.

To unravel the contribution of nutrition to cancer, the biological processes underpinning cancer development need to be understood as this will help in ultimate cancer prevention and treatment. Deoxyribonucleic acid (DNA) is the ultimate critical macromolecule in carcinogenesis. Cancer is caused by accumulated mutations in a single cell, resulting in its uncontrolled proliferation. In a cell, there are two copies of most genes; one from each chromosome in a pair and in order for a gene to stop working completely and potentially lead to cancer, both copies must be mutated. Carcinogenesis is usually a multistep Process that can be discussed in the context of such fundamental changes, in cell physiology that together determine malignant phenotype, as oncogenes, mutated tumour-suppressors genes, inappropriately-activated telomerase, mutated genes that regulate apoptosis and epigenetic perturbation.

- **Oncogenes**

This is a sequence of DNA that has been altered or mutated from its original form, the Proto-oncogene, causing a spontaneous cell proliferation. Proto-oncogenes are normal genes that control a cell growth and division by coding for proteins that pass the message in a succession from the exterior of the cell to its nucleus. Most haematological and solid tumours are caused by either activation of certain genes that promote carcinogenesis, normally called oncogenes. Oncogenes are responsible for production of transcription factors, growth factors, receptors, genes involved with chromatin remodelling and apoptosis regulatory factors. It is generally accepted that oncogenes are main cancer causing genes.

- **Tumour Suppressor Genes**

Tumour suppressor genes are genes that regulate the growth of cells. When these genes are functioning properly, they can prevent and inhibit the growth of tumours. There are 3 main types of tumour suppressor genes, namely, one that slows down and stops cells division; one that fixes damages in DNA when cells divide and the third is the one that stimulates cells death, apoptosis. They encode for proteins that are involved in inhibiting the proliferation of cells crucial to normal development and differentiation and thus enables them to stop the uncontrolled growth of cancer cells. However genetic damage or mutation that occurs to these genes may contribute to the development of a cancerous tumour. Several tumour suppressor genes have been investigated for a role in aetiology of cancer; for example loss-of-function mutation in a tumour suppressor gene NF1, which encodes Neurofibromin (a Ras GTPase-activating protein; RasGAP) has been reported as a cause of inherited cancer known as neurofibromatosis type 1. Neurofibromatosis type 1 has been associated with development of glioma. It has been shown that NF1 is generated during cell cycle progression and degraded by Ras induced activation of protein kinase C (PKC); hence, inhibition of PKC resulted in accumulation and stabilization of NF1 in different human glioblastoma cells in vitro. Also, it is widely known that retinoblastoma protein encoded byorgan, such as the lung, the tumour is called metastatic breast cancer, not lung cancer. Retinoblastoma gene is involved in cell cycle regulation in the retina. Meanwhile, a mutation in the tumour suppressor gene RB which is

constitutively expressed in non-neoplastic cells has been associated with retinoblastoma – a childhood retinal cancer.

- **Genes that Regulate Apoptosis.**

Apoptosis is a programmed cell death that normally involved in an organism's development and maintenance. Apoptosis may be induced when a cell becomes abnormal especially during tumour and perhaps malignancy therein causing the abnormal cell to die. However, the abnormal cell can fail to die due to mutation that leads either to malfunctioning of such a tumour suppressor gene as p53 gene, a gene that can trigger apoptosis, or over-expression of such proto-oncogene as bcl-2 which produces large quantities of bcl-2 protein which inactivate apoptotic programme. Malignant lymphomas resulting from transformed B-lymphocyte are caused by the mutation of bcl-2 gene.

- **Telomerase Activities.**

This is RNA-associated enzyme that synthesis telomeres, specialized sequences of DNA found at the tip of chromosomes which prevent the continuous loss of DNA during the course of replication in a cell. A normal cell has a replication span, and stops dividing when old. Telomeres partly regulate the process of ageing and dying of a cell as they shorten every time chromosomes are replicated and the cell divides. Once telomeres become shortened to a certain size, the cell reaches a crisis point and then prevented from dividing further and dies thereby serving as tumour suppressor by inducing cell death. Conversely, the shortening of telomeres in a cell undergoing replication can be prevented either by oncogenic expression or inactivation of tumour suppression activity as in a cell undergoing malignant transformation. In the transformed cell, telomeres do shorten but as the crisis point nears, an enzyme telomerase which was formerly inactive become activated and thus prevents telomeres from shortening further thereby prolonging the life of the cell. Indeed, telomerase activity has been detected in more than 90% of human tumours including breast, colon, prostate and ovarian cancers. Telomerase may also act to promote tumour-genesis by mechanisms that do not depend on telomere length. Thus, telomerase activity and maintenance of telomere length are essential for the maintenance of replicative potential in cancer cells. In normal cells, once the telomeres are shortened beyond a certain point, the loss of telomere function leads to activation of p53-dependent cell-cycle checkpoints, causing proliferative arrest or apoptosis. However, transformed cells may have defects in cell-cycle checkpoints, allowing for critical telomere shortening in dividing cells. These cells may die by apoptosis or survive with chromosome defects that cause genomic instability. Reactivation of telomerase in cells with abnormal genomes confers an unlimited proliferative capacity to cells that have tumouri-genic potential.

- **Epigenetic Perturbations**

This is the process by which gene expression can be altered without changing the DNA sequence. More recently it has become clear that epigenetic alterations in the CpG islands near the promoter regions of tumour suppressor genes may also contribute to genetic instability. Many published studies have shown that epigenetic alterations at the loci that control different specific transcription factors may result in miss-interpretation of some histone codes and producing factors that can dysregulate cell cycle control machinery and cause cancer. For example, the carcinogenic potentials of the fusion of carboxyl terminal of Plant homeo-domain (PHD) fingers (JARIDIA) with the trans-activating domain of nucleoporin 98 (NUP98) to produce JARIDIA –NU98 has been studied. This study found that cells transfected with

JARDIA – NU98 fusion gene (a gene commonly seen in acute myeloid leukemia) proliferated indefinitely compared with the controls transfected with empty vectors. The study shows that chromosomal instability resulting from translocations may lead to production of factors that can disrupt methylation status or methylation-readout areas of some important loci in the DNA and cause cancer. Thus epigenetic perturbation may have some important implication in cancer initiation.