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Question One: What do you understand by primary or simple obesity?

 Obesity results when caloric intake exceeds energy expenditure. A crude population measure of obesity is the body mass index (BMI), a person’s weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI of 30 or more is generally considered obese.

Question Two: How does congenital and drug therapy affect obesity?

 Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Drugs such as steroids and some antidepressants may also cause weight gain. It is essential that the medications are used in conjunction with healthy eating; physical activity, and behaviour modification, as medication usage without such changes are generally ineffective. The decision to initiate drug therapy in overweight individuals should be made after consideration of the risks and benefits and the goals of drug therapy should be clear.

GOALS OF THERAPY

The goal of any treatment (including drug therapy) for overweight individuals is long-term weight reduction (and maintenance of the weight loss) and improvement in overall health. Available drugs treating obesity could be divided into three categories:

* The first one is the group of drugs that suppress appetite (eg. sibutramine);
* the second is the group of drugs that interfere with digestion (eg. orlistat);
* and the third category is an inhomogeneous group of drugs that are actually used for other indications than weight loss, but with a concomitant weight loss effect.

 Such drugs are for example incretins used in the treatment of diabetes (eg. exenatide, liraglutide), antiepileptic drugs (eg. topimarate) and antidepressants (eg. fluoxetin, sertaline).

Obesity and Congenital syndromes

 Constitutional obesity and mental retardation co-occur 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. Life span for children with congenital heart disease is less than normal. Congenital and acquired coronary disease and underlying vascular abnormalities in childhood are likely to be exacerbated by obesity, which is independently associated with endothelial dysfunction and hypertension.

 Activity restriction in children with congenital heart disease was associated with the development of obesity. Even children who were of healthy weight at baseline had a higher risk of becoming obese over time if their activity was restricted. Physical activity limitation is a risk factor unique to children with heart disease. Importantly, physical activity restrictions in children with heart disease are not solely determined by practitioner recommendations. Indeed, these limitations may sometimes be initiated by parents or be self-imposed. Children with heart disease are often sedentary even when not limited by their physiology.

 Massin in a study reported recently that children who had undergone the arterial switch operation were much less likely than their peers to participate in moderate or vigorous activity even when no restrictions had been placed by their cardiologists. Decreased activity may lead to deconditioning, decreased exercise capacity, and lower quality of life. A sedentary lifestyle associated with congenital heart disease is known to carry into adulthood and predict increased morbidity and mortality in this population. Several recent studies have shown the benefits of physical training programs in both adults and children with congenital heart disease.

 Practitioners may need to refocus counselling during outpatient visits, providing careful instructions for appropriate and safe exercise regimens with regard to the underlying condition, in addition to more traditional counselling regarding exercise restrictions. Given the fact that patients with acquired and congenital heart disease have not escaped the epidemic of obesity, it is especially important for practitioners to adapt current activity guidelines.

 Genes and behavior may both be needed for a person to be overweight. In some cases, multiple genes may increase one’s susceptibility for obesity and require outside factors; such as abundant food supply or little physical activity. Families can’t change their genes but they can change the family environment to encourage healthy eating habits and physical activity. Those changes can improve the health of family members—and improve the family health history of the next generation.

* However, genes can directly cause obesity in specific disorders such as Bardet-Biedl syndrome and Prader-Willi syndrome. Prader-Willi syndrome, the commonest obesity syndrome is due to loss of imprinted genes on 15q11-13.

**Question Three**: Outline the Aetiology of Cancer and its Molecular Basis

Cancer risk factors

 As a rule, carcinogenesis is a process caused not by a single factor but by collaborative action of several agents.

*Major carcinogenic factors:*

1. Chemical carcinogens (tobacco, asbestos, etc.)
2. Radiation (UV, ionising)
3. Oncogenic viruses

*Other risk factors*

1. Diet
2. Chronic infections [helicobacter pylori (stomach), hepatitis C and B viruses (liver), human papillomaviruses (HPV; cervix, oral?)]
3. Genetic predisposition

Smoking, which is responsible for approx. 25-30% of all cancer deaths, is the *preventable risk factor* with a major significance. Diet is, presumably, a similarly significant risk factor. Approx. 20-40% of all cancer deaths are caused by an *unbalanced diet*, ie general over-nutrition, too many animal fats, and reduced intake of certain vitamins, minerals and fibres of fresh fruit and vegetables. Further risk factors include infections, genetic predisposition, alcohol abuse, occupational exposition to carcinogenic agents and environmental effects, such as solar irradiation as well as indoor exposition to radon, and passive smoking.

**Chemical carcinogens**

The carcinogenic effect of all chemical substances is based on their ability to react with intracellular macromolecules, especially DNA and RNA, and thus induce malfunctions in the cells. The primary targets of chemical carcinogens are the oncogenes and tumour suppressor genes. Chemical carcinogens are broadly divided into two classes: ***complete*** (initiator + promoter) and the more frequently occurring ***incomplete*** (only initiator) agents. Their action may be ***direct*** or ***indirect*** (procarcinogens – activation after metabolic conversion). The carcinogenic effect of pro-carcinogens is primarily dependent on the site of their metabolic conversion. With ubiquitary enzymes, carcinogenesis occurs at the site of entrance (e.g. benzo[a]pyrene in tobacco smoke, metabolic conversion in the lungs, bronchial carcinoma). Substances that require organ-specific enzymes for metabolic conversion, e.g. aromatic amines (conversion at first in the liver, then in the kidney, carcinogenic effect only in the urinary bladder) will induce malignancy far away from the entrance

**Major chemical carcinogens in humans**

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| Carcinogenic substance | Tumour | Source |
| *Direct-acting carcinogens* |
| *Alkylating agents:* |   |   |
| Cyclophosphamide | Leukaemia, lymphoma | Cytostatic drugs |
| *Indirect-acting carcinogens* |
| *Polycyclic aromatic hydrocarbons*: |   |   |
| Carbon black, tar, mineral oilsbenzo[a]pyrene | Skin cancerBronchial carcinoma | Occupational exposition,Cigarette smoke |
| *Aromatic amines, azo dyes:* |   |   |
| 2-naphthylaminebenzidine (butter yellow)2-acetylaminofluorene | Urinary bladder cancerLiver cancer | Rubber industryDye industry |
| *Nitrosamines and nitrosamides:* |   |   |
| Dimethyl-,Diethylnitrosamine | Stomach, colon, liver cancer | Nitrates and nitrites in food (preservatives),Fertilisers,Tobacco smoke |
| *Organic substances/solvents:* |   |   |
| Vinyl chloridebenzene | Liver angiosarcoma, glioblastoma,Leukaemia | PVC productionChemical industry |
| *Anorganic substances:* |   |   |
| Arsenic | Skin, bronchial, liver cancer | Ore extraction,Heat technology,Construction industry, mining,Fossil fuel refinery |
| Asbestos | Mesothelioma, bronchial carcinoma |
| Chromium | Bronchial carcinoma |
| Nickel | Carcinoma of the nasal cavity |
| *Biological substances:* |   |
| Aflatoxin B1Diethylstilbestrol | Liver cancerEndometrial cancer | Aspergillus flavus (fungus)Synthetic oestrogen |

**Risk behaviour: Smoking and chronic alcohol abuse**

***Tobacco*** is by far the most important risk factor for oral cancer and pre-cancer. Tobacco is smoked, chewed or sniffed worldwide. Processed tobacco contains at least 3050 compounds, many of which are toxic and/or carcinogenic. Besides aromatic hydrocarbons (e.g. benzo[a]pyrene), the tobacco-specific N-nitrosamines (TSNA) are the major carcinogens. TSNAs are ***causative agents*** for **oral cancer** and precancer (oral **leukoplakias**). Cigarette smoke is also directly associated with the development of **laryngeal and bronchial carcinoma**. Moreover, about one third of all cancer-related deaths worldwide are attributed to smoking. Smokers have a significantly increased risk of developing cancer, not only in the upper and lower respiratory tract but also in the following organs:

* Stomach
* Esophagus
* Bladder
* Kidney
* Pancreas
* Uterine cervix
* Breast
* Colon

A correlation between smoking and *leukaemia* is also discussed. Beside the increased risk of cancer, the hazard of developing diseases of the cardiovascular system and the lungs is generally recognised. The number of tobacco-related deaths in Germany is more than 100,000 per year; approx. 50% of smokers die of smoking-related diseases. The ***early starting age*** (at present ***13.5 years***) gives rise to particular concern.

Currently, extensive anti-smoking campaigns are run in countries of the European Union including information, counselling and therapy for smoking cessation.

**In these programmes, active participation of dentists, oral and maxillo-facial surgeons is indispensable.**

While most people are aware of the dangers of smoking, awareness of the **consequences of alcohol abuse** for the development of malignant tumours, particularly oral and pharyngeal carcinomas, is lacking. The risk for smokers who do not drink alcohol is twice to four times as high as that for non-smokers; this risk is increased 5 to 15-fold with excessive smoking and alcohol consumption (alcohol increases the permeability of the oral mucosa, thus intensifying the carcinogenic effect of smoking). Three glasses of wine a day are also supposed to increase the risk in non-smokers by factor. Results of a metaanalysis of all epidemiological data available so far on the hazardous effects of mild, moderate, or heavy chronic alcohol abuse suggest an increasing rate of cancer. Every drink taken on an average daily basis (mean alcohol content approx. 10 g) increases the risk of a malignancy by 5 to 30%, with the highest risk being that of oral, pharyngeal, or oesophageal tumours (Longnecker MP & Engner S. 1996)

**Radiation carcinogenesis**

All types of shortvawe radiation, especially ionising radiation, can cause cancer. Principally, the effects of ionising radiation and ultraviolet rays are distinguished.

*Mechanism of damaging action*

The carcinogenic effect of radiation is related to its mutagenic effects, e.g. damage to DNA through the surrounding hydrogen molecules. Water molecules will be split by photons into free radicals (H+,OH-,e-) which will finally damage the DNA.

The radiation energy

* Causes chromosome breakage, translocation and point mutations
* Changes the protein structure
* Inactivates enzymes
* Destroys membranes.

**Ultraviolet rays (UV)**

*Effect of UV rays on skin:*

* Inactivation of enzymes
* Inhibition of cell division
* Activation of T-suppressor cells
* Activation of tumour suppressor gene p53
* Induction of mutations
* Cell death

The most common types of UV-induced skin tumours are:

* Squamous cell carcinoma (epidermis)
* Malignant melanoma (melanocytes)
* Basocellular carcinoma (pluripotent stem cell?)

The melanin pigment in melanocytes provides protection against UV-radiation. Therefore, malignant melanoma occurs more rarely in people with dark skin than in fair-skinned individuals. Albinos and patients with xeroderma pigmentosum (defect of a DNA-repair gene) are at extremely high risk of developing UV-related tumours.

**Ionising radiation (alpha, beta and gamma rays)**

* Alpha rays consist of protons and neutrons
* Beta rays consist of electrons
* Gamma rays include photons and X-rays

The carcinogenic effect of ionising radiation depends on:

* Type of radiation (alpha rays are more dangerous than gamma)
* Dose-incidence relation
* DNA-repair mechanisms
* Host factors (age, immune status, hormones, tissue characteristics)

Hierarchy of radiation sensitivity between different organs:

1. Testis/ovaries
2. Bone marrow (leukaemia)
3. Thyroid gland
4. Gastro-intestinal tract
5. Breast
6. Lung
7. Salivary gland tissues
8. Skin
9. Bone

***Note!***

* Survivors of radiation catastrophes (Hiroshima, Nagasaki, Chernobyl) disclosed a markedly increased incidence of: myeloid leukaemia (bone marrow), carcinomas of the thyroid gland, breast and lung.
* Many physicians from the early X-ray era died of radiation-induced cancers.

**Oncogenic viruses**

**RNA viruses**

The oncogenic RNA viruses are referred to as ***retroviruses*** since they contain a reverse transcriptase (in the infected cell, a virus DNA is synthetised by the virus RNA which will be incorporated into the host genome).

Two types are distinguished:

1. Acute transforming retroviruses
2. Slow transforming retroviruses

**Human retrovirus infections (tumours)**

* Human T-cell leukaemia/lymphoma virus (HTLV) type I and III
* HTLV-III is identical with the causative agent of AIDS (HIV=human immunodeficiency virus). Its association with human malignancies is indirect: Kaposi’s sarcoma, malignant non-Hodgkin lymphomas, leukaemias.

Despite their high number, the role of retroviruses in human carcinogenesis has so far only been proved in the above-mentioned two tumours.

**Oncogenic DNA viruses**

They are mainly responsible for the development of malignant tumours in humans. Some viruses are particularly characteristic for certain diseases. The mechanisms of the neoplastic effect of DNA viruses are manifold: some of them, like HPV, include transforming sequences (oncogenes) which will be incorporated into the host genome, others have an indirect effect. HPV gene sequences can be detected in some oropharyngeal carcinomas, particularly those of the tonsils and the larynx. Their role in the development of these tumours is the subject of research.

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| Virus family | Type | Tumour |
| Papavo Virus | Human Papilioma Virus: | Verruca vulgaris |
| Different types (1, 2, 4, and 7) |
| Types 6, 8, 11 (low-risk) | Genital warts (condyloma acuminatum)Laryngeal papilloma |
| Types 16, 18, 31, 33 (high-risk) | Cervical carcinomaOro-pharyngeal carcinomaLaryngeal carcinoma |
| Herpes viruses | Type 2 herpes-simplex virus(HSV-2) | Cervical carcinomaVulvar carcinoma |
| Epstein-Barr virus(EBV) | Malignant B-cell lymphoma(Burkitt-lymphoma)Hodgkin lymphomaNasopharyngeal carcinoma |
| Human herpes virus 8(HHV-8) | Kaposi's sarcoma |
| Hep-a-DNA viruses | Hepatitis B virus (HBV) | Hepatocellular carcinoma |
| Hepatitis C virus | Hepatocellular carcinoma |

**Molecular basis of cancer**

It is a multi-step process that requires the accumulation of many genetic changes over time. These genetic alterations involve activation of proto-oncogenes to oncogenes, deregulation of tumour suppressor genes and DNA repair genes and ‘immortalisation’.

### Cell cycle regulation and the importance of apoptosis

In normal cells, proliferation and progression through the cell cycle is strictly regulated by groups of proteins that interact with each other in a specific sequence of events (Figure 2). Checkpoints ascertain that individual stages of the cell cycle are completed correctly and ensure that incompletely replicated DNA is not passed onto daughter cells. Core to this control system are cyclin-dependent kinases (CDKs). CDKs are ‘master protein kinases’ that drive progression through the different phases of the cell cycle by phosphorylating and activating other downstream kinases. CDK activity is dependent on the presence of activating subunits called cyclins which are synthesised and degraded in a cell cycle-dependent manner. Cyclin-CDK complexes are further tightly regulated by CDK inhibitors.



**Figure 2: Cyclins and cyclin-dependent kinases (CDKs) regulate the cell cycle.** CDK’s and their regulatory subunits, cyclins (A, B, D & E) tightly control transition through the cell cycle. The brackets indicate the periods in which the cyclin-CDK complexes are active and orchestrate all events necessary in this period. The **restriction point** (R point) is a point in G1 at which the cell becomes ‘committed’ to the cell cycle and after which extracellular proliferation signals are no longer required.

The re-entry of cells into the cell cycle is decided at the **restriction point (R point)**. This decision is influenced by extracellular mitogenic signals which are transmitted via signalling pathways to key regulatory proteins, such as transcription factors (e.g. E2F) in the nucleus (refer to Figure 3, Section 2). These regulatory proteins ultimately activate the S-phase CDKs, which trigger the start of DNA synthesis.

In normal cells, activation of another transcription factor, p53, often referred to as the ‘guardian of the genome’, can impose cell cycle arrest and induce apoptosis (programmed cell death) through its ability to:

* induce the expression of cell cycle inhibitors to prevent proliferation of a cell until any damage has been repaired or
* Initiate apoptosis, if the genomic damage is too great and cannot be repaired.

In >50% of all human tumours the p53 pathway is aberrant. Inactivation of the p53 protein renders it unable to signal and activate the cell’s apoptotic machinery resulting in increased survival of cancer cells.

### Cell immortalisation and tumourigenesis

Immortalisation is defined as the acquisition of an infinite lifespan. Normal mammalian **somatic** cells proliferate a limited number of times before undergoing senescence. Senescent cells may remain metabolically active even though they have permanently ceased proliferation. Immortalisation is an essential step in the malignant transformation of normal cells and can be attributed, in part, to the presence of **telomerase**, the enzyme responsible for maintaining telomeres at the ends of chromosomes. By extending telomeric DNA, telomerase is able to counter the progressive telomere shortening that would otherwise lead to cell death. Unlike normal cells that lack detectable levels of telomerase activity, approximately 90% of human tumours consist of cells that contain an active telomerase enzyme.