I. One of the few cancers that is increasing world-wide in both incidence and mortality is thyroid cancer.

1. (2 pts) What is a major risk factor for thyroid cancer?
   
   Nuclear radiation exposure

2. (2 pts) Large increases in thyroid cancer occurred after what catastrophic event in Russia in 1986, and how does this support your answer to the first question above?
   
   Chernobyl nuclear plant meltdown \( \rightarrow \) spread of nuclear radiation, and populations closest had 100-fold increased incidence of thyroid cancer

3. (3 pts) Other than dietary iodine, there is no other dietary factor associated with thyroid cancer. Describe in general the kind of epidemiological (population) study that would test for a role for fat in the diet (for example) in thyroid cancer incidence.
   
   Compare populations from regions of low fat diets with those in regions of high fat diets, in particular those who migrate from regions of low fat diets, in terms of the incidence of thyroid cancer

4. (8 pts) In some thyroid cancers, a germ-line mutation in the ret growth factor receptor gene is found, and in thyroid adenomas (like polyps in color cancer) mutations in the thyroid stimulating hormone (TSH) receptor and two protooncogenes, gsp and ras, are observed. In thyroid carcinomas, additional point mutations are observed in a tyrosine kinase (trk) gene, and B-raf transforming growth factor gene, as well as several mutations in the p53 gene and erbB epidermal growth factor receptor genes. Describe a process for the development of thyroid cancers based on all the factors described in 1-4 above.

   Thyroid cancer, like most cancers, is a multifactorial, multistage process that requires both genetic and epigenetic cellular changes to progress to invasive cancer. Based on the information above, initiation by an inherited germ-line mutation in the ret growth factor gene may predispose an individual to thyroid cancer along with nuclear radiation exposure. Nuclear radiation may also be involved in promotion of it causes mutations in the TSH receptor gene and conversion of the two protooncogenes, gsp and ras to their activated oncogenes.

   Thus, promotion occurs with clonal expansion of the initiated cells. Progression to an invasive tumor then can apparently occur through mutations to additional growth factor genes (trk and B-raf) as well as loss of p53 tumor suppressor activity via mutations in the p53 tumor suppressor gene. Any one or all of these mutations may occur as a result of nuclear radiation exposure or other unknown viral, chemical, dietary, etc. factor.
II. Aflatoxin (A) is a potent natural carcinogen found in moldy peanuts and some moldy grains. Aflatoxin was in the news this past year because it was found as a contaminant in some commercial dog food, and resulted in deaths of several dogs who ate the food.

\[ \text{Aflatoxin (A)} \]

1. (6 pts) Based on the structure of epoxide B, draw the structure of the most likely DNA adduct C and show mechanistically (arrow convention) how C is formed from B.

2. (6 pts) Give two possible reasons why aflatoxin is a potent carcinogen. Any 2 of:
   1) Relatively flat planar structure → intercalation into DNA
   2) Reactive 8+ or oxecarboxylic ion site for attack by DNA-Nu.
   3) Pseudo bay region and non-aromatic epoxide formed that is stable enough to get into the nucleus.

III. Tamoxifen is an antitumor drug used both as a preventative and in the adjuvant treatment of breast cancer.

1. (4 pts) Describe the mechanism of action of tamoxifen.

Tamoxifen and metabolites bind to estrogen receptors → abnormal DNA binding → depletion of estrogen receptor required for the growth of most breast tumors.

2. (5 pts) A woman who is taking the anticoagulant warfarin (Coumadin) comes in for a prescription of tamoxifen. What should you do, and why?

Ask her if her anticoagulation status is being monitored carefully while her new drug (tamoxifen) is introduced. Tamoxifen is an inhibitor of cytochromes P450 that could thereby decrease metabolism of warfarin to inactive metabolites → possible bleeding.

3. (6 pts) What newer class of antiestrogen drugs have been found to be superior to tamoxifen for treatment of breast cancer, what is their mechanism of action, and why are they superior?

Aromatase inhibitors that ↓ synthesis of estrogens, especially in breast tumors where aromatase is up-regulated. Compared to tamoxifen, these inhibitors cause less incidence of clots, strokes and uterine cancers.
IV. A common form of brain cancer, glioblastoma, is usually treated by irradiation and by using a chemotherapy regimen of the hydrazine alkylating agent, Procarbazine, the nitrosourea alkylating agent, Lomustine, and the antimitotic drug, Vincristine.

1. (6 pts) What part of the cell cycle does each agent target?
   - Procarbazine – intermitotic phase
   - Lomustine – intermitotic phase
   - Vincristine –纺丝 phase

2. (6 pts) What are the major toxicities of each of these antitumor drugs?
   - Procarbazine – BMD + sterility
   - Lomustine – BMD + pulmonary fibrosis
   - Vincristine – peripheral neuropathy

3. (12 pts) Describe in words the mechanism of action of each agent.
   - Procarbazine – A produg that is metabolized to diazonium ion that alkylates DNA.
   - Lomustine – A produg that cross-links DNA via diazonium and aziridinum ions.
   - Vincristine – Binds to tubulin dimers → blocks polymerization of microtubules → inhibition of mitosis at metaphase.

4. (5 pts) Based on your answers to the above questions, would you consider this to be a good combination chemotherapy regimen, and why or why not?
   Overall this is a reasonably good regimen since there is good cell cycle coverage and only 2 of the drugs cause BMD. Mechanistically, the two DNA damaging agents act in different ways as well.

5. (7 pts) Temozolamide (Temodar) is a produg of another agent, Dacarbazine, that is often added to the regimen above as part of outpatient therapy. Explain why the produg was developed and describe its mechanism of action.
   This produg was developed to enhance absorption and first-pass liver metabolism. It is hydrolyzed to a triazene that methylates DNA.
V. Procarbazine (Matulane) is an antitumor agent that finds special use in the highly successful combination chemotherapy of Hodgkins lymphomas. Below is a partial scheme for the metabolism of procarbazine to one of its active alkylating agents.

\[
\begin{align*}
\text{CH}_3\text{-N=O-C=H} + \text{H-O-H} &\rightarrow \text{CH}_3\text{-N=N-C-H} + \text{H}_2\text{O} \\
\text{CH}_3\text{-N=N-C-H} + \text{H}_2\text{O} &\rightarrow \text{CH}_3\text{-N=N-C-H} + \text{H}_2\text{O} \\
\end{align*}
\]

1. (2 pts) Metabolism of A to B by P450 is the first step in the very common drug metabolism pathway called oxidatively dealkylation.

2. (5 pts) Show mechanistically (arrow convention) how B is converted to C and D and give the structure of C. 

3. (5 pts) Show mechanistically how D undergoes an elimination reaction to give E and F and give the structure of E. 

4. (5 pts) Show mechanistically how F methylates DNA and give the structure of the product G. Compound F is a diazomethane ion.

5. (5 pts) A cancer patient who you know is taking procarbazine has a flu-like cold, and is about to purchase an OTC cold remedy. What should you check and why?

Whether or not any sympathomimetic amines are present in the cold remedy. Procarbazine can inhibit the enzyme MAO that metabolizes sympathomimetic amines to inactive metabolites. Concentration of these amines which can lead to heart arrhythmias.