



PATHOLOGY

● Suggested Clinical Cases

Neoplastic Disorders

PBD9 Chapter 7 and PBD8 Chapter 7: Neoplasia

BP9 Chapter 5 and BP8 Chapter 6: Neoplasia

1 A 40-year-old man has a positive stool guaiac test during a routine physical examination. A colonoscopy is performed and a 0.9-cm, circumscribed, pedunculated mass on a short stalk is found in the upper rectum. Which of the following terms best describes this lesion?

- A Adenoma
- B Carcinoma
- C Choristoma
- D Hamartoma
- E Hyperplasia
- F Sarcoma

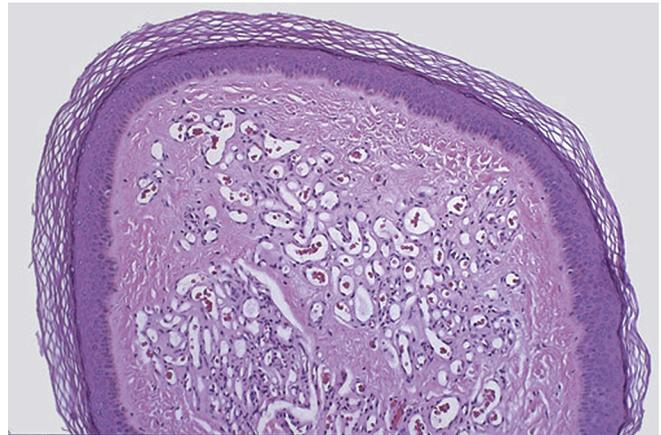
2 A 32-year-old woman has experienced dull pelvic pain for the past 2 months. Physical examination shows a right adnexal mass. An abdominal ultrasound scan shows a 7.5-cm cystic ovarian mass. The mass is surgically excised. The surface of the mass is smooth, and it is not adherent to surrounding pelvic structures. On gross examination, the cystic mass is filled with hair. Microscopically, squamous epithelium, tall columnar glandular epithelium, cartilage, and fibrous connective tissue are present and resemble normal tissue counterparts. Which of the following is the most likely diagnosis?

- A Adenocarcinoma
- B Fibroadenoma
- C Glioma
- D Hamartoma
- E Mesothelioma
- F Rhabdomyosarcoma
- G Teratoma

3 A 62-year-old man has had several episodes of hematuria in the past week. He has a 48 pack-year history of smoking cigarettes. On physical examination, there are no abnormal findings. A urinalysis shows 4+ hematuria, and cytologic examination of the urine shows that atypical cells are present. A cystoscopy is performed and a 4-cm sessile mass with a

nodular, ulcerated surface is seen in the dome of the bladder. Which of the following terms best describes this lesion?

- A Adenoma
- B Carcinoma
- C Fibroma
- D Papilloma
- E Sarcoma

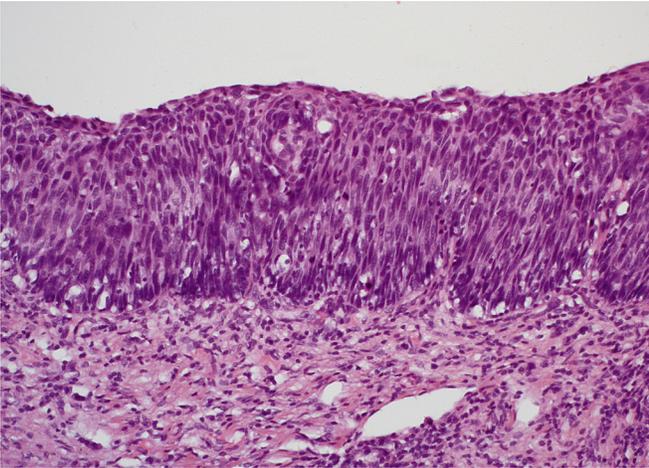


4 A 23-year-old woman has noted a nodule on the skin of her upper chest. She reports that the nodule has been present for many years and has not changed in size. It is excised, and the microscopic appearance is shown in the figure. Which of the following neoplasms is this lesion most likely to be?

- A Fibroadenoma
- B Hemangioma
- C Leiomyoma
- D Lipoma
- E Melanoma
- F Nevus

5 A 50-year-old woman undergoes screening colonoscopy as part of a routine health maintenance work-up. An isolated 1-cm pedunculated polyp is found in the sigmoid colon. The excised polyp histologically shows well-differentiated glands with no invasion of the stalk. Which of the following investigational research procedures can distinguish most clearly whether the polyp represents hyperplasia of the colonic mucosa or a tubular adenoma?

- A Flow cytometry to quantitate cells in the S phase
- B Histochemical staining for mucin
- C Immunohistochemical staining for keratin
- D Molecular marker of clonality

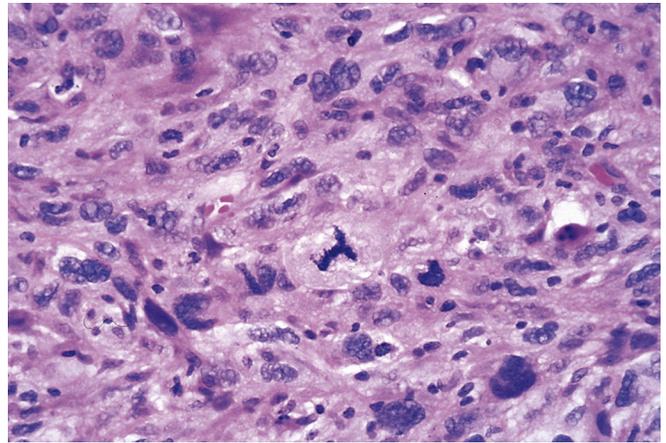


6 A 39-year-old woman underwent a routine health maintenance examination for the first time in many years. A Pap smear was obtained, and the result reported was abnormal. On pelvic examination, a red, slightly raised, 1-cm lesion on the anterior ectocervix at the 2 o'clock position was excised and biopsied. The microscopic appearance on medium-power magnification is shown in the figure. Which of the following is most characteristic of this patient's condition?

- A Primary neoplasm in the endometrium
- B Elevated CA-125 level in the serum
- C Positive HSV-2 molecular test in the lesion
- D Pulmonary nodules on a chest radiograph
- E No recurrence following local excision

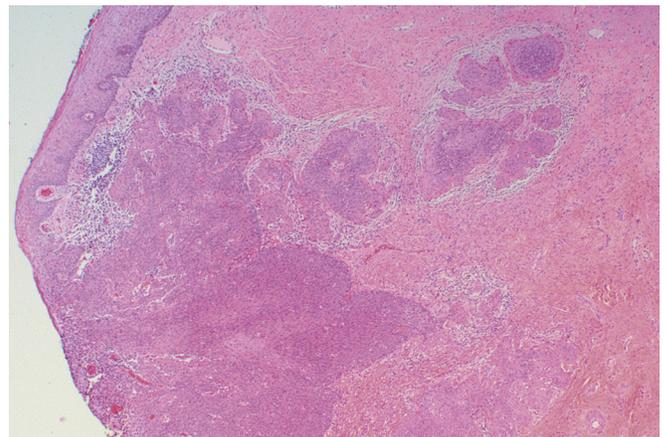
7 A 53-year-old woman has noticed increasing malaise. On physical examination, there are no abnormal findings, but a stool guaiac test is positive. Her hemoglobin level is 7.9 g/dL. A colonoscopy is performed, and a 3-cm sessile mass is found in the cecum. A biopsy specimen of the mass shows a moderately differentiated adenocarcinoma confined to the mucosa. An abdominal CT scan shows no lymphadenopathy or hepatic lesions. Given this information, which of the following is the best course of action?

- A Administer a multiagent chemotherapeutic regimen
- B Observe the lesion for further increase in size
- C Remove the entire colon to prevent a recurrence
- D Resect the tumor and some normal surrounding tissue
- E Search for a primary malignancy in another organ



8 A 57-year-old woman has experienced an increasing feeling of fullness in her neck along with a 3-kg (7-lb) weight loss over the past 3 months. On physical examination, there is a firm, fixed mass in a 3 × 5 cm area in the right side of the neck. A CT scan shows a solid infiltrating mass in the region of the right lobe of the thyroid gland. A biopsy of the mass is performed and the microscopic appearance is shown in the figure. All areas of the tumor have similar morphology. Which of the following terms best describes this neoplasm?

- A Anaplastic
- B Apoptotic
- C Dysplastic
- D Metaplastic
- E Well-differentiated



9 A Pap smear obtained from a 29-year-old woman during a routine health maintenance examination is abnormal. She is currently asymptomatic. She has a history of multiple sexual partners. Cervical biopsy specimens are obtained and the microscopic appearance is shown in the figure. Which of the following is the most likely diagnosis?

- A Adenocarcinoma
- B Carcinoma in situ
- C Dysplasia
- D Hamartoma
- E Metaplastic transformation
- F Squamous cell carcinoma

10 A 44-year-old woman feels painless lumps in her armpit, which were not present a month ago. On examination, right axillary lymphadenopathy is present. The nodes are painless but firm. Which of the following is the most likely lesion in her right breast?

- A Acute mastitis with abscess
- B Fibroadenoma
- C Infiltrating lobular carcinoma
- D Intraductal carcinoma
- E Leiomyosarcoma



11 A 69-year-old woman has experienced increasing malaise and a 10-kg weight loss over the past year. She dies of massive pulmonary thromboembolism. The gross appearance of the liver at autopsy is shown in the figure. Which of the following best describes the lesions seen in her liver?

- A Invasive angiosarcoma
- B Hepatocellular carcinoma
- C Leukemic infiltration
- D Metastatic adenocarcinoma
- E Multifocal hepatic adenomas

12 A 66-year-old man with chronic cough has an episode of hemoptysis. On physical examination, there are no abnormal findings. A chest radiograph shows a 6-cm mass in the right lung. A sputum cytologic analysis shows neoplastic squamous cells. Metastases from his lung lesion are most likely to be found at which of the following sites?

- A Cerebral hemisphere
- B Chest wall muscle
- C Hilar lymph nodes
- D Splenic red pulp
- E Vertebral bone marrow

13 An epidemiologic study of cancer deaths recorded in the last half of the 20th century is conducted. The number of deaths for one particular type of cancer had been decreasing in developed nations, despite the absence of widespread screening and prevention programs. Which of the following neoplasms was most likely to be identified by this study?

- A Cerebral glioma
- B Gastric adenocarcinoma
- C Hepatic angiosarcoma
- D Leukemia
- E Pulmonary small cell carcinoma

14 An epidemiologic study of cancer deaths recorded in the last half of the 20th century is conducted. The number of deaths for one particular cancer had increased markedly in developed nations. More than 30% of cancer deaths in men, and more than 24% of cancer deaths in women, were caused by this neoplasm in 1998. In some nations, prevention strategies reduced deaths from this cancer. Which of the following neoplasms was most likely identified by this study?

- A Cerebral glioma
- B Bronchogenic carcinoma
- C Hepatocellular carcinoma
- D Colonic adenocarcinoma
- E Pancreatic adenocarcinoma
- F Skin melanoma

15 An epidemiologic study analyzes health care benefits of cancer screening techniques applied to persons more than 50 years of age. Which of the following diagnostic screening techniques used in health care is most likely to have the greatest impact on reduction in cancer deaths in Europe and North America?

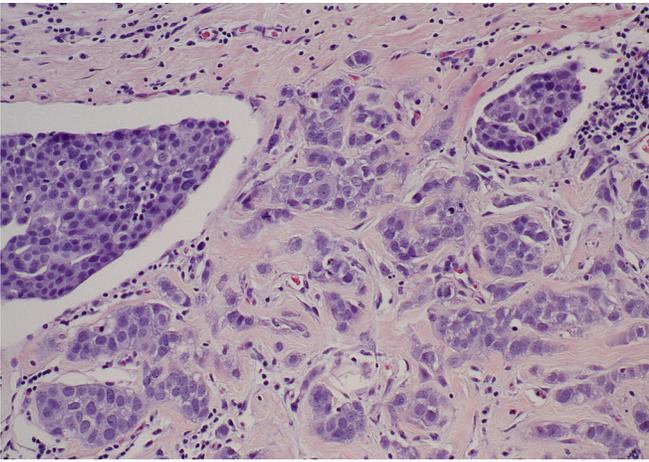
- A Chest radiograph
- B Mammography
- C Pap smear
- D Serum tumor markers
- E Stool guaiac
- F Urine cytology

16 A 38-year-old woman has abdominal distention that has been worsening for the past 6 weeks. An abdominal CT scan shows bowel obstruction caused by a 6-cm mass in the jejunum. At laparotomy, a portion of the small bowel is resected. Flow cytometric analysis of a portion of the tumor shows a clonal population of B lymphocytes with high S phase. Translocation with activation of which of the following nuclear oncogenes is most likely to be present in this tumor?

- A *APC*
- B *EGF*
- C *MYC*
- D *p53*
- E *RAS*

17 A 50-year-old woman has had easy fatigability and noted a dragging sensation in her abdomen for the past 5 months. Physical examination reveals that she is afebrile. She has marked splenomegaly, but no lymphadenopathy. Laboratory studies show her total WBC count is 250,000/mm³ with WBC differential count showing 64% segmented neutrophils, 11% band neutrophils, 7% metamyelocytes, 5% myelocytes, 4% myeloblasts, 3% lymphocytes, 2% basophils, 2% eosinophils, and 2% monocytes. A bone marrow biopsy is performed, and karyotypic analysis of the cells reveals a t(9;22) translocation. Medical treatment with a drug having which of the following modes of action is most likely to produce a complete remission in this patient?

- A Activating cellular caspases
- B Antibody binding to EGF receptors
- C Delivering normal *p53* into cells with viral vectors
- D Inhibiting tyrosine kinase activity
- E Preventing translocation of β -catenin to the nucleus



18 A 54-year-old woman notes a lump in her right breast. Physical examination shows a 2-cm mass fixed to the underlying tissues beneath the areola and three firm, nontender, lymph nodes palpable in the right axilla. There is no family history of cancer. An excisional breast biopsy is performed, and microscopic examination shows the findings in the figure. Over the next 6 months, additional lymph nodes become enlarged, and CT scans show nodules in the lung, liver, and brain. Which of the following molecular abnormalities is most likely to be found in her carcinoma cells?

- A Amplification of the *ERBB2* (*HER2*) gene
- B Deletion of one *RB* gene copy
- C Fusion of *BCR* and *C-ABL* genes
- D Inactivation of one *BRCA1* gene copy
- E Mutation of one *p53* gene copy

19 The mother of a 5-year-old boy notices that his abdomen has enlarged in the past 6 months. On physical examination there is an ill-defined abdominal mass. An abdominal CT scan shows a 9-cm mass in the region of the right adrenal gland. The mass is removed and microscopically shows primitive hyperchromatic cells. Cytogenetic analysis of tumor cells shows many double minutes and homogeneously staining regions. Which of the following genes is most likely to have undergone alterations to produce these findings?

- A *BCL1* (cyclin gene)
- B *BCL2* (anti-apoptosis gene)
- C *IL2* (growth factor gene)
- D *K-RAS* (GTP-binding protein gene)
- E *Lyn* (tyrosine kinase gene)
- F *N-MYC* (transcription factor gene)

20 A 34-year-old sexually active woman undergoes a routine physical examination. There are no abnormal findings. A Pap smear is obtained as part of the pelvic examination. Cytologically, the cells obtained on the smear from the cervix show severe epithelial dysplasia (high-grade squamous intraepithelial lesion). Which of the following therapeutic options is most appropriate for this woman?

- A Antibiotic therapy
- B Excision
- C Ovarian removal
- D Screening of family members
- E Watchful waiting

21 An epidemiologic study investigates the potential morphologic and molecular alterations that may contribute to the development of cancers in a population. Data analyzed from resected colonic lesions show changes that suggest the evolution of a sporadic colonic adenoma into an invasive carcinoma. Which of the following best describes the mechanism producing these changes leading to colonic malignancies?

- A Activation of proto-oncogenes by chromosomal translocation
- B Extensive regeneration of tissues increasing the mutation rate in regenerating cells
- C Inheritance of defects in *TP53* genes that increase the susceptibility to develop cancer
- D Overexpression of growth factor receptor genes
- E Stepwise accumulation of multiple proto-oncogene and tumor suppressor gene mutations

22 A 61-year-old woman has noted a feeling of pelvic heaviness for the past 6 months. On physical examination, there is a palpable nontender lower abdominal mass. An abdominal ultrasound scan shows a 12-cm solid mass in the uterine wall. A total abdominal hysterectomy is performed. The mass has the microscopic appearance of a well-differentiated leiomyosarcoma. One year later, a chest radiograph shows a 4-cm nodule in her right lower lung. Cytologic analysis of a fine-needle biopsy specimen of the nodule shows a poorly differentiated sarcoma. The patient's medical history indicates that she has smoked cigarettes most of her adult life. Which of the following mechanisms best explains these findings?

- A Continued cigarette smoking by the patient
- B Development of a second primary neoplasm
- C Inheritance of a defective *RB* gene
- D Immunodeficiency with HIV infection
- E Metastasis from an aggressive tumor subclone

23 A 70-year-old woman reported a 4-month history of a 4-kg weight loss and increasing generalized icterus. On physical examination, she has midepigastic tenderness on palpation. An abdominal CT scan shows a 5-cm mass in the head of the pancreas. Fine-needle aspiration of the mass is performed. On biochemical analysis, the neoplastic cells show continued activation of cytoplasmic kinases. Which of the following genes is most likely to be involved in this process?

- A *APC*
- B *MYC*
- C *p53*
- D *RAS*
- E *RET*
- F *sis*

24 A 22-year-old man has a raised, pigmented lesion on his forearm that has increased in size and become more irregular in color over the past 4 months. Physical examination shows a 0.5 × 1.2 cm black-to-brown asymmetric lesion with irregular borders. An excisional biopsy specimen shows clusters of pleomorphic pigmented cells that extend into the reticular dermis. Family history indicates that the patient's maternal uncle died from a similar tumor. His grandfather required enucleation of the left eye because of a "dark brown" retinal mass. Which of the following genes is most likely to have undergone mutation to produce these findings in this family?

- A *BCL2* (anti-apoptosis gene)
- B *c-MYC* (transcription factor gene)
- C *IL2* (growth factor gene)
- D *Lyn* (tyrosine kinase gene)
- E *p16* (cell cycle inhibition)
- F *p53* (DNA damage response gene)

25 A 3-year-old child has exhibited difficulty with vision in her right eye. On physical examination, there is leukocoria of the right eye, consistent with a mass in the posterior chamber. MR imaging shows a mass that nearly fills the globe. The child undergoes enucleation of the right eye. Molecular analysis of the neoplastic cells indicates absence of both copies of a gene that contributes to control of the cell cycle. Which of the following genes has most likely undergone mutation in this neoplasm?

- A *BCR-ABL*
- B *BCL2*
- C *hMSH2*
- D *K-RAS*
- E *NF1*
- F *p53*
- G *RB*

26 A 76-year-old man has experienced abdominal pain for the past year. On physical examination, there is an epigastric mass. An abdominal CT scan shows a 10-cm mass in the body of the pancreas. A fine-needle biopsy specimen of this mass shows a moderately differentiated adenocarcinoma. Mutational analysis of the carcinoma cells shows inactivation of cyclin-dependent kinase inhibitor with loss of growth-suppression. Regulatory pathways controlled by which of the following genes are most likely altered in this man's carcinoma?

- A *BCL2*
- B β -Catenin
- C *MYC*
- D *p53*
- E TGF- β

27 A 55-year-old man has had hemoptysis and worsening cough for the past month. On physical examination, wheezes are auscultated over the right lung posteriorly. A chest radiograph shows a 6-cm right perihilar mass. A fine-needle aspiration biopsy is performed and yields cells with the microscopic appearance of non-small cell bronchogenic carcinoma. Molecular analysis of the neoplastic cells shows a *p53* gene mutation. Which of the following mechanisms has most likely produced the neoplastic transformation?

- A Inability to hydrolyze GTP
- B Growth factor receptor activation
- C Loss of cell cycle arrest
- D Microsatellite instability
- E Transcriptional activation

28 A 26-year-old man with a family history of colon carcinoma undergoes a surveillance colonoscopy. It reveals hundreds of polyps in the colon, and two focal 0.5-cm ulcerated areas. A biopsy specimen from an ulcer reveals irregularly shaped glands that have penetrated into the muscular layer. Which of the following molecular events is believed to occur very early in the evolution of his colonic disease process?

- A Activation of the WNT signaling pathway
- B Inability to hydrolyze GTP-bound RAS
- C Loss of heterozygosity affecting the *p53* gene
- D Mutations in mismatch repair genes.
- E Translocation of *BCL2* from mitochondria to cytoplasm

29 A 63-year-old man has a cough with hemoptysis for 10 days. He has a 65 pack-year history of smoking. A chest CT scan shows a 5-cm right hilar mass. Bronchoscopy is performed, and lung biopsy specimens show small cell anaplastic lung carcinoma. His family history shows three first-degree maternal relatives who developed leukemia, sarcoma, and carcinoma before age 40 years. Which of the following gene products is most likely to have been altered by mutation to produce these findings?

- A *APC* (tumor suppressor)
- B *BCL2* (anti-apoptosis)
- C *K-RAS* (GTP binding)
- D *NF1* (GTPase activation)
- E *p53* (DNA damage response)

30 A 30-year-old man has a 15-year history of increasing numbers of benign skin nodules. On physical examination, the firm, nontender, subcutaneous nodules average 0.5 to 1 cm. Further examination shows numerous oval 1- to 5-cm flat, light brown skin macules. Ophthalmoscopic examination shows hamartomatous nodules on the iris. A biopsy specimen of one skin nodule shows that it is attached to a peripheral nerve. Which of the following molecular abnormalities is most likely related to his clinical presentation?

- A Decreased susceptibility to apoptosis
- B Impaired functioning of mismatch repair
- C Increased production of epidermal growth factor
- D Lack of nucleotide excision repair
- E Persistent activation of the *RAS* gene
- F Reduced expression of *RB* protein

31 A 53-year-old man diagnosed with oral cancer and treated with radiation and chemotherapy 1 year ago now has a positron emission tomography (PET) scan of his neck that shows a single focus of increased uptake. This focus is resected and microscopic examination shows that it is a metastasis. Molecular analysis of this cancer shows *p53*, *PTEN*, and *c-MYC* gene mutations. Which of the following metabolic pathways is most likely up-regulated to promote his cancer cell survival and proliferation?

- A Aerobic glycolysis
- B Gluconeogenesis
- C Hexose monophosphate shunt
- D Oxidative phosphorylation
- E Purine degradation

32 A 49-year-old man has a lump near his right shoulder that has been increasing in size for the past 8 months. On physical examination, a 4-cm, firm, nontender mass is palpable in the right supraclavicular region. The mass is excised, and microscopically it shows a lymphoid neoplasm. Karyotypic analysis of the cells shows a chromosomal translocation, t(14;18), bringing the immunoglobulin heavy chain gene together with another gene. Which of the following genes is most likely activated by this translocation?

- A *APC* (tumor suppressor gene)
- B *BCL2* (anti-apoptosis gene)
- C *BRCA1* (DNA repair gene)
- D *c-MYC* (transcription factor gene)
- E *IL2* (growth factor gene)
- F *K-RAS* (GTP-binding protein gene)

33 A 40-year-old man notices an increasing number of lumps in his groin and armpit over the past 5 months. On physical examination, he has generalized nontender lymph node enlargement and hepatosplenomegaly. An inguinal lymph node biopsy specimen shows a malignant tumor of small, well-differentiated lymphoid cells. Immunostaining of the tumor cells with antibody to *BCL2* is positive in the lymphocytic cell nuclei. Which of the following mechanisms has most likely produced this lymphoid neoplasm?

- A Diminished apoptosis
- B Gene amplifications
- C Increased tyrosine kinase activity
- D Loss of cell cycle inhibition
- E Reduced DNA repair

34 In an experiment, cells from human malignant neoplasms explanted into tissue culture medium continue to replicate. This allows development of “immortal” tumor cell lines that are extremely useful for the study of tumor biology and responses to therapeutic modalities. Activation of which of the following molecular components is most likely to endow these tumor cells with limitless replicative ability in vivo and in vitro?

- A Hypoxia-induced factor 1
- B *BCL2* gene
- C Cyclin-dependent kinase gene methylation
- D DNA replication repair
- E Telomerase

35 A 60-year-old man has noted a nodule in his neck that has increased rapidly in size over the past 2 months. On physical examination, there is a firm, nontender, 10-cm mass in the left lateral posterior neck that appears to be fused cervical lymph nodes. Hepatosplenomegaly is noted. A head CT scan reveals a mass in the Waldeyer ring near the pharynx. A biopsy of the neck mass is performed, and on microscopic examination shows abnormal lymphoid cells with many mitotic figures and many apoptotic nuclei. He is treated with a cocktail of cell cycle-acting chemotherapeutic agents. The cervical and oral masses shrink dramatically over the next month. Based on his history and response to treatment, the tumor cells are most likely to have which of the following features?

- A Diminished vascularity
- B Evolution of polyclonality
- C High growth fraction
- D Limited capacity to metastasize
- E Strong expression of tumor antigens

36 A 30-year-old man has a pheochromocytoma of the left adrenal gland; a sibling had a cerebellar hemangioblastoma. He undergoes adrenalectomy, and on microscopic examination there is extensive vascularity of the neoplasm. Mutational analysis of the neoplastic cells shows that both allelic copies of a gene have been lost, so that a protein that binds to hypoxia-inducible factor 1- α is no longer ubiquitinated, but instead translocates to the nucleus and activates transcription of *VEGF*. Which of the following genes is most likely mutated in this man?

- A *APC*
- B *BCL2*
- C *EGF*
- D *HER2*
- E *HST1*
- F *MYC*
- G *VHL*

37 A 48-year-old woman notices a lump in her left breast. On physical examination she has a firm, nonmovable, 2-cm mass in the upper outer quadrant of the left breast. There are enlarged, firm, nontender lymph nodes in the left axilla. A fine-needle aspiration biopsy is performed, and the cells present are consistent with carcinoma. A lumpectomy with axillary lymph node dissection is performed, and carcinoma is present in two of eight axillary nodes. Reduced expression of which of the following molecules by the tumor cells is most likely responsible for the lymph node metastases?

- A Estrogen receptors
- B ERBB2 (HER-2)
- C E-cadherin
- D Progesterone receptors
- E Tyrosine kinases

38 A 55-year-old woman has felt an enlarging lump in her left breast for the past year. A hard, irregular 5-cm mass fixed to the underlying chest wall is palpable in her left breast. Left axillary nontender lymphadenopathy is noted. There is no hepatosplenomegaly. A chest CT scan reveals multiple bilateral pulmonary “cannonball” nodules. A left breast biopsy is performed, and on microscopic examination shows high-grade infiltrating ductal carcinoma. The appearance of the nodules in her lungs is most likely related to which of the following?

- A Internal mammary artery invasion by carcinoma cells
- B Lymphatic connections between the breast and the pleura
- C Overexpression of estrogen receptors within the carcinoma cell nuclei
- D Proximity of the breast carcinoma to the lungs
- E Pulmonary chemokines that bind carcinoma cell chemokine receptors

39 A study of colonic polyps is performed. Malignant cells localized to the polyp are compared to those from polyps showing invasion of the stalk. Molecular analysis shows up-regulation of certain molecules in the invasive malignant cells. Invasive lesions are more likely to exhibit lymphatic metastases. Which of the following markers is most likely to have increased expression in the invasive malignant epithelial cells?

- A BCL2
- B CD44
- C EGFR
- D RAS
- E Vimentin

40 In a clinical trial, patients diagnosed with malignant melanoma are treated by infusion of autologous CD8+ T cells grown in vitro. These CD8+ T cells are known to kill melanoma cells, but not normal cells. Which of the following target antigens in the tumor cells are most likely recognized by these CD8+ T cells?

- A Class I MHC molecules with a melanoma cell peptide
- B Class I MHC molecules with a peptide from normal melanocytes and melanoma cells
- C Class I MHC molecules plus a peptide derived from carcinoembryonic antigen
- D Class II MHC molecules with a melanoma cell peptide
- E Class II MHC molecules with a peptide from normal melanocytes and melanoma cells
- F Class II MHC molecules with laminin receptors on melanoma cells

41 An experiment involving carcinoma cells grown in culture studies the antitumor surveillance effects of the innate immune system. These carcinoma cells fail to express MHC class I antigens. It is observed, however, that carcinoma cells are lysed when an immune cell that has been activated by IL-2 is added to the culture. Which of the following immune cells is most likely to function in this manner?

- A CD4+ lymphocyte
- B CD8+ lymphocyte
- C Macrophage
- D Neutrophil
- E NK cell
- F Plasma cell

42 A 33-year-old man has experienced occasional headaches for the past 3 months. He suddenly has a generalized seizure. CT scan of the head shows a periventricular 3-cm mass in the region of the right thalamus. A stereotactic biopsy of the mass yields large lymphoid cells positive for B cell markers. Which of the following underlying diseases is most likely to be found in this patient?

- A Diabetes mellitus
- B HIV infection
- C Hypertension
- D Multiple sclerosis
- E Tuberculosis

43 An investigational study reviews cells harvested from patients 30 to 50 years of age who had right-sided colon cancer with multiple polyps present. These patients typically develop multiple malignant lesions of the colon during middle age. Molecular analysis of the cells from the lesions shows changes in *hPMS1*, *hPMS2*, and *hMLH1* genes. Which of the following principles of carcinogenesis is best illustrated by this study?

- A Carcinogenesis is a multistep process
- B Inability to repair DNA is carcinogenic
- C Many oncogenes are activated by translocations
- D Tumor initiators are mutagenic
- E Tumor promoters induce proliferation

44 A 12-year-old girl and a 14-year-old boy have developed skin nodules in predominantly sun-exposed areas of their skin over the past 5 years, but their six siblings have not. On physical examination, both children are of appropriate height and weight. The skin lesions are 1- to 3-cm maculopapular nodules that are erythematous to brown-colored and have areas of ulceration. Microscopic analysis of biopsy specimens of the skin lesions shows squamous cell carcinoma. The children have no history of recurrent infections, and their parents and other relatives are unaffected. Which of the following mechanisms is most likely to produce neoplasia in these children?

- A Inherited mutation of the *p53* gene
- B Chromosomal translocation
- C Failure of nucleotide excision repair of DNA
- D Ingestion of food contaminated with *Aspergillus flavus*
- E Infection with human papillomavirus

45 A 26-year-old woman has a lump in her left breast. On physical examination, she has an irregular, firm, 2-cm mass in the upper inner quadrant of the breast. No axillary adenopathy is noted. A fine-needle aspirate of the mass shows anaplastic ductal cells. The patient's 30-year-old sister was recently diagnosed with ovarian cancer, and 3 years ago her maternal aunt was diagnosed with ductal carcinoma of the breast and had a mastectomy. Mutation involving which of the following genes is most likely present in this family?

- A *BCL2* (anti-apoptosis gene)
- B *BRCA1* (DNA repair gene)
- D *ERBB2* (growth factor receptor gene)
- E *HST1* (fibroblast growth factor gene)
- F *IL2* (growth factor gene)
- G *K-RAS* (GTP-binding protein gene)

46 In a study of patients with non-Hodgkin B cell lymphoma, a nuclear gene is found to be actively transcribed to mRNA and is transported into the cell cytoplasm. A protein is translated from this mRNA, with up-regulation of BCL2. In a control group without lymphoma, translation of the mRNA does not occur. How is the silencing of this active gene's mRNA most likely to occur?

- A Absence of tRNA
- B Binding to miRNA
- C Methylation of DNA
- D Mutation of mRNA
- E Up-regulation of mtDNA

47 A study of patients treated with chemotherapy protocols for cancer shows that 10% of them subsequently develop a second cancer, a much higher incidence compared with a control group not receiving chemotherapy. These chemotherapy protocols included the alkylating agent cyclophosphamide. What is the most likely mechanism by which this agent causes carcinogenesis in these treated cancer patients?

- A Activation of protein kinase C
- B Activation of endogenous viruses
- C Blockage of TGF- β pathways
- D Direct DNA damage
- E Inhibition of DNA repair
- F Inhibition of telomerase

48 A 51-year-old man who works in a factory that produces plastic pipe has experienced weight loss, nausea, and vomiting over the past 4 months. On physical examination, he has tenderness to palpation in the right upper quadrant of the abdomen, and the liver span is increased. Laboratory findings include serum alkaline phosphatase, 405 U/L; AST, 45 U/L; ALT, 30 U/L; and total bilirubin, 0.9 mg/dL. An abdominal CT scan shows a 12-cm mass in the right lobe of the liver. A liver biopsy is performed, and microscopic examination shows a malignant neoplasm of endothelial cells. The patient has most likely been exposed to which of the following agents?

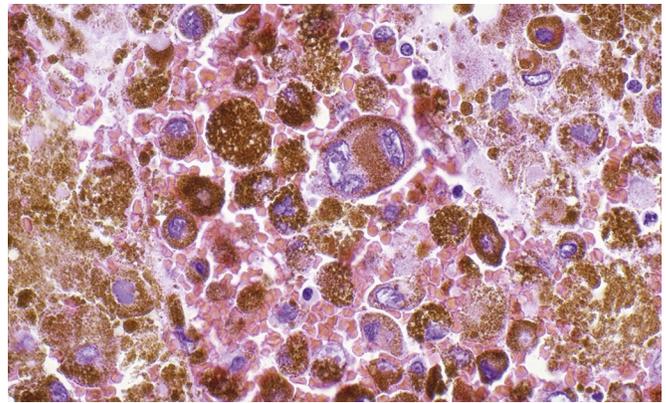
- A Arsenic
- B Asbestos
- C Benzene
- D Beryllium
- E Nickel
- F Vinyl chloride
- G Naphthalene

49 A 56-year-old woman has had vaginal bleeding for 1 week. Her last menstrual period was 10 years ago. On physical examination, a lower abdominal mass is palpated. An endometrial biopsy is performed and shows endometrial carcinoma. An abdominal CT scan shows a 6-cm mass in the left ovary. A total abdominal hysterectomy is performed. Microscopically, the ovarian mass is a granulosa-theca cell tumor producing estrogen. Which of the following best describes the relationship between these two neoplasms?

- A Genetic susceptibility to tumorigenesis
- B Mutational inactivation of a tumor suppressor gene
- C Paraneoplastic syndrome
- D Promotion of carcinogenesis
- E Tumor heterogeneity

50 A 23-year-old woman, who works as a secretary for an accounting firm in Kiev, has noted a palpable nodule on the side of her neck for the past 3 months. On physical examination, there is a 2-cm, firm, nontender nodule involving the right lobe of the thyroid gland. Sequencing of DNA derived from the nodule shows rearrangement of the *RET* gene. No other family members are affected by this disorder. Which of the following findings would be considered most relevant in this woman's medical history?

- A Chronic dietary iodine deficiency
- B Chronic ethanol abuse
- C Congenital ataxia telangiectasia
- D Ingestion of arsenic compounds
- E Radiation exposure in childhood

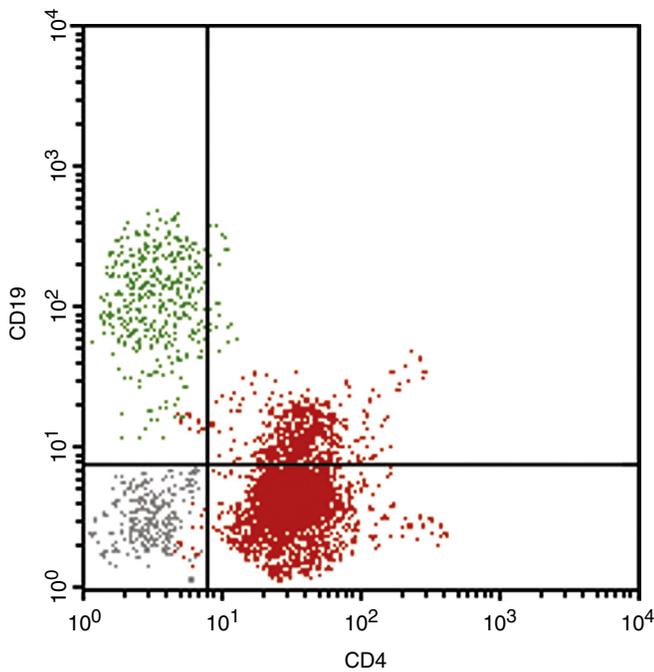


51 A 42-year-old man is concerned about a darkly pigmented "mole" on the back of his hand. The lesion has enlarged and bled during the past month. On physical examination, there is a slightly raised, darkly pigmented, 1.2-cm lesion on the dorsum of the right hand. The lesion is completely excised. The microscopic appearance is shown in the figure. Which of the following factors presents the greatest risk for the development of this neoplasm?

- A Allergy to latex
- B Asbestos exposure
- C Chemotherapy
- D Smoking tobacco
- E Ultraviolet radiation

52 A 33-year-old woman with multiple sexual partners has had vaginal bleeding and discharge for the past 5 days. On physical examination, she is afebrile. Pelvic examination shows an ulcerated lesion arising from the squamocolumnar junction of the uterine cervix. A cervical biopsy is performed and microscopic examination reveals an invasive tumor containing areas of squamous epithelium, with pearls of keratin. In situ hybridization shows the presence of human papillomavirus type 16 (HPV-16) DNA within the tumor cells. Which of the following molecular abnormalities in this tumor is most likely related to infection with HPV-16?

- A Functional inactivation of the RB protein
- B Increased expression of epidermal growth factor receptor
- C Epigenetic silencing of the *RB* gene
- D Inability to repair DNA damage
- E Trapping of the RAS protein in a GTP-bound state



53 A 66-year-old woman has worked all of her life on a small family farm on the Kantō Plain near Tokyo. She has had no previous major illnesses, but has been feeling increasingly tired and weak for the past year. On physical examination, she is afebrile, but appears pale. Laboratory studies show hemoglobin, 11.3 g/dL; hematocrit, 33.8%; platelet count, 205,200/mm³; and WBC count, 64,000/mm³. Immunophenotyping of her leukocytes yields the findings shown in the figure. Assuming that the dominant cell population is clonal, which of the following microbial agents is most likely involved in this patient's disease process?

- A Epstein-Barr virus
- B Hepatitis B virus
- C HIV-1
- D *Helicobacter pylori*
- E Human T cell lymphotropic virus type 1

54 A 40-year-old man has a history of intravenous drug use. Physical examination shows needle tracks in his left antecubital fossa. He has mild scleral icterus. Serologic studies for HBsAg and anti-HCV are positive. He develops hepatocellular carcinoma 15 years later. Which of the following viral characteristics best explains why this patient developed hepatocellular carcinoma?

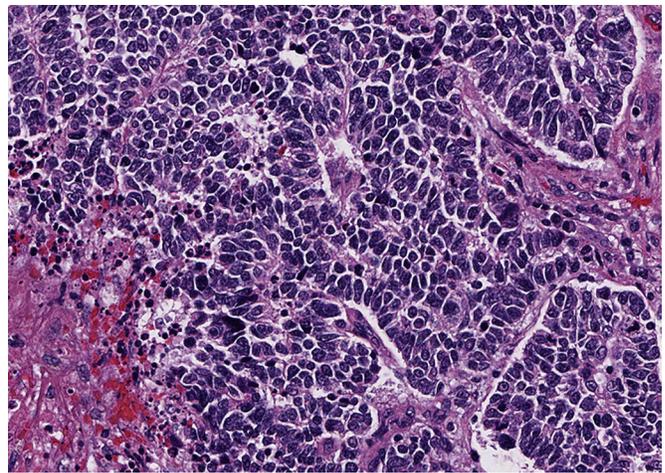
- A Viral integration in the vicinity of proto-oncogenes
- B Viral capture of proto-oncogenes from host cellular DNA
- C Viral inflammatory changes with genomic damage
- D Viral inactivation of *RB* and *p53* gene expression
- E Viral infection of inflammatory cells with host immunosuppression

55 A 61-year-old man with a history of chronic viral hepatitis has noted a 6-kg weight loss over the past 5 months. Physical examination shows no masses or palpable lymphadenopathy. An abdominal CT scan shows a nodular liver with a 10-cm mass in the right lobe. A stool guaiac test result is negative. An elevation in which of the following laboratory tests is most likely to be present in this man?

- A Alpha-fetoprotein
- B CA-19-9
- C Calcitonin
- D Carcinoembryonic antigen
- E Immunoglobulin M

56 A clinical study involves patients diagnosed with carcinoma whose tumor stage is T4N1M1. The patients' survival rate 5 years from the time of diagnosis is less than 50%, regardless of therapy. Which of the following clinical findings is most likely to be characteristic of this group of patients?

- A Cachexia
- B Cardiac murmur
- C Icterus
- D Loss of sensation
- E Splenomegaly
- F Tympany



57 A 49-year-old man experiences an episode of hemoptysis. On physical examination, he has puffiness of the face, pedal edema, and systolic hypertension. A chest radiograph shows an irregular perihilar 5-cm mass of the right lung. Laboratory studies show normal serum electrolytes. A transbronchial biopsy is performed, and the microscopic findings are shown in the figure. A bone scan shows no metastases. Immunohistochemical staining of the tumor cells is most likely to be positive for which of the following?

- A Antidiuretic hormone
- B Corticotropin
- C Erythropoietin
- D Insulin
- E Parathyroid hormone-related peptide

58 A 59-year-old man has noticed blood in his urine for the past week. Cystoscopy shows a 4-cm exophytic mass involving the right bladder mucosa near the trigone. After biopsy specimens are obtained, he undergoes a radical cystectomy. Examination of the excised specimen shows an anaplastic carcinoma that has infiltrated the bladder wall. Which of the following techniques applied to the cells from his neoplasm is most likely to categorize the cell of origin?

- A Chromosomal karyotyping
- B Cytologic smear
- C DNA microarray
- D Flow cytometric analysis
- E Immunohistochemistry

59 A 69-year-old man has noted a chronic cough for the past 3 months. On physical examination, there is mild stridor on inspiration over the right lung. A chest radiograph shows a 5-cm right hilar lung mass, and a fine-needle aspiration biopsy specimen of the mass shows cells consistent with squamous cell carcinoma. If staging of this neoplasm is denoted as T2N1M1, which of the following findings is most likely in this man?

- A Brain metastases
- B Elevated corticotropin level
- C Infiltration of the chest wall
- D Obstruction of a mainstem bronchus
- E Poorly differentiated tumor cells

60 A 76-year-old woman has reported a change in the caliber of her stools during the past month. On physical examination, there are no abnormal findings, but a stool sample is positive for occult blood. A colonoscopy is performed and a constricting mass involving the lower sigmoid colon is found. She undergoes a partial colectomy. Which of the following techniques used during surgery can best aid the surgeon in determining whether the resection is adequate to reduce the probability of a recurrence?

- A Electron microscopy
- B Fine-needle aspiration
- C Flow cytometry
- D Frozen section
- E Radiologic imaging
- F Serum carcinoembryonic antigen assay

ANSWERS

1 A A discrete small mass such as that described is probably benign. Adenomas arise from epithelial surfaces. Though adenocarcinoma may arise from a colonic adenoma, such malignant lesions tend to be larger and more irregular. A choristoma is a benign mass composed of tissues not found at the site of origin. A hamartoma is a rare benign mass composed of tissues usually found at the site of origin. A hyperplastic colonic lesion tends to be smaller and flatter. A sarcoma is a malignant neoplasm arising in mesenchymal tissues, not in epithelium.

PBD9 266–268 BP9 162–163 PBD8 260 BP8 174–175

2 G A teratoma is a neoplasm derived from totipotential germ cells that differentiate into tissues that represent all three germ layers: ectoderm, endoderm, and mesoderm. When the elements all are well differentiated, the neoplasm is “mature” (benign). Adenocarcinomas have malignant-appearing glandular elements. Fibroadenomas have a benign glandular and stromal component; they are common in the breast. Gliomas are found in the central nervous system. Hamartomas contain a mixture of cell types common to a tissue site; the lung is one site for this uncommon lesion. A mesothelioma arises from the lining of thoracic and abdominal body cavities. A rhabdomyosarcoma comprises cells that poorly resemble striated muscle; most arise in soft tissues.

PBD9 267–268 BP9 163–164 PBD8 261–262 BP8 175

3 B A large, irregular, ulcerated mass such as that described is most likely malignant, and the epithelium of the bladder gives rise to carcinomas. Urothelial carcinomas are associated with smoking. An adenoma is a benign epithelial neoplasm of glandular tissues. A fibroma is a benign mesenchymal neoplasm. A papilloma is a benign, localized mass that has an exophytic growth pattern. A sarcoma is derived from cells of mesenchymal origin; sarcomas are much less common than carcinomas.

PBD9 269–271 BP9 163–164, 199 PBD8 263–265 BP8 176–179

4 B The small, discrete nature of this mass and its slow growth with nearly unchanged size suggest a benign neoplasm. The red color is consistent with vascularity. A hemangioma is a common benign lesion of the skin. Fibroadenomas arise in the breast. Leiomyomas, which are white, arise from smooth muscle and are most common in the uterus. Lipomas are yellow fatty tumors that can occur beneath the epidermis. Melanomas are malignant and tend to increase in size quickly; many are darkly pigmented. The benign counterpart to the melanoma is the nevus, which is quite common, but nevi are usually light to dark brown.

PBD9 268, 271 BP9 162, 164 PBD8 263 BP8 174–176

5 D A true neoplasm is a monoclonal proliferation of cells, whereas a reactive proliferation of cells is not monoclonal. Molecular genetic analysis, such as allelotype analysis with microsatellite markers, shows clonality. Reactive and neoplastic cellular proliferations may have similar histochemical and immunohistochemical staining patterns based on the type of cells and proteins that are present. Flow cytometry is effective at indicating the DNA content, aneuploidy, and growth fraction, but does not indicate clonality.

PBD9 267–270, 334 BP9 167, 212–213 PBD8 276–278 BP8 185–186

6 E The figure shows an in situ carcinoma of the squamous cervical epithelium with neoplastic growth only above the basement membrane. Tissue damage with repair and regeneration may give rise to metaplasia, which may progress to dysplasia, considered premalignant. In situ cancers, limited to the epithelium, are noninvasive, and local excision has a 100% cure rate. In situ lesions do not give rise to metastases and have not arisen elsewhere. This lesion is related to human papillomavirus (HPV) infection, not herpes simplex virus (HSV). CA-125 is most often a tumor marker for ovarian cancer.

PBD9 271–272 BP9 166 PBD8 264 BP8 177–178

7 D A malignant epithelial neoplasm arises in the mucosa but has a tendency to invade locally. A benign neoplasm is often well circumscribed, and compressed normal surrounding tissue appears to form a discrete border. This localized lesion can be resected easily, with adequate margins. Without evidence for spread outside the colon, chemotherapy is unlikely to be of benefit. The biopsy specimen shows a malignant lesion; it must be removed before it increases in size and invades locally or metastasizes. If there is no family history, a familial cancer with high risk of recurrence from multiple polyps is unlikely; local excision is adequate. Such a solitary mucosal lesion is unlikely to represent a metastasis.

PBD9 268–272 BP9 167–168 PBD8 268–269 BP8 174–177

8 A The cells shown in the figure show marked pleomorphism and hyperchromatism (anaplasia), and it is difficult to discern the cell of origin because no differentiation is noted. A bizarre tripolar mitotic figure is present. This degree of anaplasia is consistent with an aggressive, high-grade malignancy called *anaplastic carcinoma*. Apoptosis is single cell necrosis, but the cells shown appear viable and not fragmented. Dysplasia refers to changes within an epithelium that presage a neoplasm. Metaplasia with one epithelial cell type substituted for another may presage dysplasia and malignancy. Well-differentiated neoplasms tend to be less aggressive and slower growing and resemble the cell of origin.

PBD9 269–270 BP9 164–166 PBD8 262–265 BP8 177–178

9 F In the figure the disorderly, atypical epithelial cells involve the entire thickness of the epithelium. They extend through the underlying basement membrane and into the underlying stroma as rounded nests at the right, a process known as *invasion*. The ectocervix and the squamous metaplasia of endocervix give rise to dysplasia from which squamous cell carcinoma can arise. Carcinoma in situ is confined to the epithelium; if the basement membrane is breached, the lesion is no longer in situ, but rather invasive. An adenocarcinoma is a malignant neoplasm arising from glandular epithelium, such as the endocervix or endometrium, not the ectocervix. A dysplastic process could precede development of carcinoma in situ and squamous carcinoma; dysplasia involves only part of the thickness of the epithelium. A hamartoma contains a mixture of cell types common to a tissue site. Metaplasia can occur in response to persistent infection with human papillomavirus (HPV) and other inflammatory conditions. Metaplasia can be the precursor to dysplasia.

PBD9 271–272 BP9 167–168 PBD8 265 BP8 177–179

10 C Lymphatic spread, especially to regional lymph nodes draining from the primary site, is typical of a carcinoma. An intraductal carcinoma has not extended beyond the basement membrane, but an infiltrating carcinoma has acquired the ability to invade and spread via metastasis. The primary site may be difficult to detect if small or deep, and hence the need for radiologic imaging, such as mammography. A fibroadenoma is a benign neoplasm and cannot invade or metastasize. Infection from a breast abscess can

spread to the lymph nodes, but the resulting nodal enlargement is typically associated with pain—a cardinal sign of acute inflammation. Sarcomas uncommonly metastasize to lymph nodes, and a leiomyosarcoma of breast is rare.

PBD9 272–273 BP9 168–169 PBD8 269–270 BP8 180

11 D The figure shows the appearance of multiple variably sized tan metastatic lesions in the liver from hematogenous spread of carcinoma. Adenocarcinomas from abdominal primary sites such as colon, pancreas, and stomach are most likely. Thromboembolism suggests a hypercoagulable state such as a paraneoplastic syndrome. Angiosarcomas of the liver are uncommon. A primary malignancy typically appears as a dominant mass, not multiple masses. Although some benign tumors, such as leiomyomas of the uterus, can be multiple, this is not the rule in the liver, and hepatic adenomas are rare. Although hepatocellular carcinomas can have “satellite” nodules, widespread nodules such as those seen in the figure are more characteristic of metastases. Leukemic infiltrates typically do not produce large mass lesions, though some lymphomas may do so. Resection of multiple metastases is usually futile.

PBD9 274 BP9 168–169 PBD8 269 BP8 179–181

12 C Carcinomas metastasize through lymphatics most often, usually to regional nodes first. Hematogenous metastases are possible, however, to sites such as bone marrow, liver, or the opposite lung. About half of all cerebral metastases arise from lung primary carcinomas. Soft-tissue metastases to muscle, fat, and connective tissues are rare, as are splenic metastases.

PBD9 273–274 BP9 168–169 PBD8 269 BP8 179–181

13 B The decrease in the number of gastric cancers may be related to reduced numbers of dietary carcinogens or a decrease in the prevalence of *Helicobacter pylori* infection; however, the exact reason is obscure. Cerebral gliomas are not as common as carcinomas; an urban legend links them to cell phone use, but legitimate epidemiologic studies have not made this link. Angiosarcomas of the liver are quite rare; they are epidemiologically linked to vinyl chloride exposure. Leukemias and lymphomas are not as common as carcinomas. Pulmonary small cell carcinomas are related to smoking, and the numbers have decreased in many countries with campaigns to reduce smoking; the death rate is typically high because the prognosis for lung cancer is so poor.

PBD9 275–277, 279 BP9 170, 204 PBD8 272, 315 BP8 214

14 B Incidence of lung cancers increased dramatically in the 20th century because of the popularity of cigarette smoking. As the number of individuals in a population who smoke increases, so do the number of lung cancers. Some cancers of the urinary tract, oral cavity, esophagus, and pancreas also are causally related to smoking. Breast, prostate, and colon cancers remain common in developed nations, but the number of cases has not increased sharply. Pap smear screening and human papillomavirus (HPV) vaccination markedly decreases numbers of cervical cancers. There has

been an increase in the incidence of melanomas worldwide, but there are still far fewer cases of melanomas than of lung cancers. Hepatic and intracranial neoplasms in adults are far less common than lung cancers.

PBD9 276–277 BP9 170 PBD8 273 BP8 182–183

15 B A screening program should reliably detect early cancers with higher incidence. Breast cancer affects up to 1 in 9 women in these regions. Mammography may aid in detection of small cancers that have a better prognosis. A chest radiograph is an insensitive technique for detecting early lung cancers. Because Pap smear screening can detect dysplasias and in situ carcinomas that can be treated before progression to invasive lesions, deaths from cervical carcinoma have steadily decreased since this screening method became widely available in the last half of the 20th century. The introduction of human papillomavirus (HPV) vaccination will diminish the numbers of cervical cancers even further. Serum tumor markers have not proved useful as general screening techniques, although they are useful in selected circumstances. Use of stool guaiac has had a minimal effect on rates of death from colorectal carcinomas, but physicians are cautioned not to indicate “rectal deferred” on the physical examination report, and hence contribute to the problem. Urine cytology is better than urinalysis for detection of urothelial malignancies, but it does not have a high sensitivity.

PBD9 276–279 BP9 170–171 PBD8 324 BP8 182

16 C The *MYC* oncogene is commonly activated in Burkitt lymphoma because of a t(8;14) translocation. The *MYC* gene binds DNA to cause transcriptional activation of growth-related genes such as that for cyclin D1, resulting in activation of the cell cycle. *EGF* (such as *HER2* in breast cancers) encodes the epithelial growth factor receptor located on the cell surface. *p53* and *APC* are tumor suppressor genes that are inactivated in many cancers, including colon cancer. *RAS* oncogene encodes a GTP-binding protein that is located under the cell membrane.

PBD9 284, 287–288 BP9 175 PBD8 284 BP8 190–191

17 D This patient has a classic history and t(9;22) translocation with chronic myelogenous leukemia. The translocation causes uncontrolled nonreceptor tyrosine kinase activity of the *BCR-ABL* fusion gene. These patients undergo remission with drugs such as imatinib that inhibit tyrosine kinases. Agents that activate caspases theoretically may help in many cases, especially when apoptosis is blocked as in tumors with *BCL2* overexpression. Antibodies to epithelial growth factor receptors, such as *ERBB2* (*HER2*) receptors, are beneficial in certain breast tumors with amplification of this gene. Delivery of *p53* into cells by viral vectors has not yet been proven to be valuable in cancer treatment, and it is not used in chronic myelogenous leukemia. Translocation of β -catenin to the nucleus occurs in colon cancers when there is mutational loss of *APC* genes.

PBD9 284, 287 BP9 174 PBD8 283–284 BP8 174

18 A Infiltrating ductal and intraductal carcinoma are present in the figure. Increased expression of *ERBB2* (*HER2*) can be detected immunohistochemically and by fluorescence in situ hybridization (FISH) in the biopsy specimen. One third of breast cancers may show this change. Such amplification is associated with a poorer prognosis. Detection of a specific gene product in the tissue has value for determination of treatment and prognosis. *BRCA1* and *p53* mutations, if inherited in the germ line, can predispose the patient to breast cancer and other tumors. With *BRCA1*, there is family history of breast cancer, often at a young age. The tumor suppressor gene *p53* mutations predispose to many types of cancers. An inherited deletion of *RB* gene predisposes to retinoblastoma. The *BCR-ABL* fusion product, seen in chronic myeloid leukemia, often results from t(9;22).

PBD9 284–285 BP9 175 PBD8 281, 324 BP8 188

19 F Double minutes and homogeneously staining regions seen on a karyotype represent gene amplifications. Amplification of the *N-MYC* gene occurs in 30% to 40% of neuroblastomas, and this change is associated with a poor prognosis. The *BCL1* and *BCL2* genes are mutated in some non-Hodgkin lymphomas. The *IL2* mutation may be present in some T cell neoplasms. *K-RAS* mutations are present in many cancers, but not typically childhood neoplasms. The *Lyn* mutation is seen in some immunodeficiency states.

PBD9 289 BP9 175 PBD8 306 BP8 190, 208

20 B Epithelial dysplasias, especially severe dysplasias, can be precursors of carcinomas. This is a key reason for Pap smear screening. The incidence of cervical carcinoma decreases when routine Pap smears are performed. Colposcopy with biopsy is indicated to determine the extent of the lesion for removal. Though related to human papillomavirus (HPV) infection, severe dysplasias are not amenable to antibiotic therapy. Ovarian neoplasms are not related to cervical dysplasias or carcinomas. In general, cervical cancers are not related to hereditary syndromes, and cervical dysplasias are not hereditary. Screening of family members is appropriate for those who have risk factors, such as multiple sexual partners. Regression of a severe dysplasia is unlikely.

PBD9 271, 333 BP9 210 PBD8 265 BP8 177–178

21 E Development of colonic adenocarcinoma typically takes years, during which time multiple mutations occur within the mucosa, including mutations involving such genes as *APC* (adenomatous polyposis coli), *K-RAS*, and *p53*. The accumulation of mutations, rather than their occurrence in a specific order, is most important in the development of a carcinoma. Activation of proto-oncogenes, extensive regeneration, faulty *TP53* genes, and amplification of growth factor receptor genes all contribute to the development of malignancies, but they are not sufficient by themselves alone to produce a carcinoma from an adenoma of the colon. Inherited loss of wild-type *TP53* contributes to multiple cancers, but not to sporadic adenomas.

PBD9 284–287, 321–322 BP9 177 PBD8 277–279, 308 BP8 197–198

22 E Although neoplasms begin as monoclonal proliferations, additional mutations occur over time, leading to subclones of neoplastic cells with various aggressive properties. This subcloning may allow metastases, greater invasiveness, resistance to chemotherapy, and morphologic differences to occur. Because sarcomas of the lung are rare, the lung mass is statistically a metastasis. Though second primary malignancies do arise, particularly in persons who have already had a malignancy, the odds favor a metastasis in a person with a prior malignancy. Sarcomas are not related to smoking tobacco. Inheritance of a mutant *RB* gene is most likely to lead to childhood retinoblastomas and osteosarcomas. Kaposi sarcoma is the sarcoma most often associated with AIDS from HIV infection.

PBD9 281–282, 321–322 BP9 177 PBD8 279 BP8 185–186

23 D The *RAS* oncogene is the most common oncogene involved in the development of human cancers. Mutations of the *RAS* oncogene reduce GTPase activity, and *RAS* is trapped in an activated GTP-bound state. *RAS* then signals the nucleus through cytoplasmic kinases. The *APC* gene can cause activation of the WNT signaling pathway. The *MYC* oncogene is a transcriptional activator that is overexpressed in many tumors. The *p53* tumor suppressor gene encodes a protein involved in cell cycle control. The *RET* proto-oncogene encodes a receptor tyrosine kinase involved in neuroendocrine cells of the thyroid, adrenal medulla, and parathyroids. The *sis* oncogene encodes platelet-derived growth factor receptor- β , which is overexpressed in certain astrocytomas.

PBD9 284–287 BP9 179–180 PBD8 282–283 BP8 188–190

24 E A family history of malignant melanoma is present. Familial tumors often are associated with inheritance of a defective copy of one of several tumor suppressor genes. In the case of melanomas, the implicated gene is called *p16*, or *INK4a*. The product of the *p16* gene is an inhibitor of cyclin-dependent kinases. Germline mutations in *CDKN2A* may also underlie familial melanomas. With loss of control over cyclin-dependent kinases, the cell cycle cannot be regulated, favoring neoplastic transformation. *BCL2* is present in some lymphoid neoplasms. The *c-MYC* gene is mutated in various carcinomas, but is not known to be specifically associated with melanomas. The *IL2* mutation is associated with some T cell neoplasms. The *Lyn* mutation is seen in some immunodeficiency states. *p53* mutations occur in many cancers, but not specifically in familial melanomas.

PBD9 291, 293 BP9 176, 182 PBD8 286–287 BP8 181–182

25 G The *RB* gene is a classic example of the two-hit mechanism for loss of tumor suppression. About 60% of these tumors are sporadic, whereas the rest are familial from inheritance of a mutated copy of the *RB* gene. Loss of the second copy in retinoblasts leads to the occurrence of retinoblastoma in childhood. The *RB* gene controls the G_1 to S transition of the cell cycle; with loss of both copies, this important checkpoint in the cell cycle is lost. The *BCR-ABL* fusion gene in chronic myelogenous leukemia is an example

of overexpression of a gene product producing neoplasia. The *BCL2* gene is an inhibitor of apoptosis. The *hMSH2* gene is present in most cases of hereditary nonpolyposis colon cancer and functions in DNA repair. Many cancers have the *K-RAS* gene, which acts as an oncogene. The *NF1* gene product acts as a tumor suppressor; this is a component of neurofibromatosis (which usually does not involve the eye), and the neoplasms typically appear at a later age. Many cancers have the *p53* tumor suppressor gene mutation, but this is not typical of childhood ocular neoplasms.

PBD9 290–293 BP9 182–184 PBD8 288–290 BP8 192–194

26 E TGF- β inhibits cell proliferation by activation of growth-inhibiting genes, such as the *CDKIs*. All pancreatic cancers and 83% of colon cancers have at least one mutational event in a TGF- β pathway. The *BCL2* family of genes acts as a regulator of apoptosis. The β -catenin pathway seen with the *APC* gene is involved with growth regulation; loss of the *APC* gene loci leads to failure in destruction of β -catenin, which translocates to the cell nucleus, where it functions as a transcription factor promoting growth. The *MYC* gene is a target of the activated *RAS* pathway. The *p53* protein is involved in tumor suppression.

PBD9 285, 293 BP9 187 PBD8 294 BP8 197–198

27 C A *p53* mutation involving both wild type alleles is one of the most common genetic alterations in human cancers, including the most common cancers—lung, colon, and breast. The loss of this tumor suppressor activity indicates that the cell cycle is not properly arrested in the late G_1 phase, and when DNA damage occurs, DNA repair cannot be completed before the cell proliferates. Inability to hydrolyze GTP is a result of *RAS* oncogene activation. Growth factors such as EGF are activators of the cell cycle to promote cell growth. Microsatellite instability occurs with mutation in genes, such as *hMSH2*, that repair DNA damage. Transcriptional activation is a feature of the *MYC* proto-oncogene.

PBD9 293–296 BP9 185–187 PBD8 290–292 BP8 195–196

28 A The patient has a classic history of familial adenomatous polyposis with numerous adenomatous polyps and malignant transformation. The earliest event in the *APC* \rightarrow adenocarcinoma sequence is loss of *APC* gene function. This prevents the destruction of β -catenin in the cytoplasm, which translocates to the nucleus and coactivates transcription of several genes. The *APC* \rightarrow β -catenin sequence is a component of the WNT signaling pathway. *RAS* activation occurs after the malignant transformation sequence is initiated by the *APC* (gatekeeper) gene. Loss of cell cycle G_1 arrest occurs with *p53* loss late in the sequence. Mutations in mismatch repair genes give rise to hereditary nonpolyposis colon cancer syndrome from loss of ability to repair DNA damage. The *BCL2* gene is not involved in the transition from adenoma to carcinoma.

PBD9 296–297 BP9 188 PBD8 292–293 BP8 197–198

29 E *p53* is the most common target for genetic alterations in human neoplasms. Most are sporadic mutations,

although some are inherited. The inheritance of one faulty *p53* suppressor gene predisposes to a “second hit” that eliminates the remaining *p53* gene. Homozygous loss of the *p53* genes dysregulates the repair of damaged DNA, predisposing individuals to multiple tumors, as in this case. The *APC* gene is mutated in sporadic colon cancers and in familial polyposis coli. The *BCL2* gene is mutated in some non-Hodgkin lymphomas. The *HER2* gene is one of the EGF receptor family members amplified in some breast cancers. The *EGF* mutation is most often seen in squamous cell carcinomas of the lung. *K-RAS* mutations are present in many cancers, but not typically in lymphoid malignancies. The *NF1* gene mutation is seen in neurofibromatosis type 1.

PBD9 293–296 BP9 185–187 PBD8 286,290 BP8 195–196,205

30 E This patient has clinical features of neurofibromatosis type 1. The *NF1* gene encodes for a GTPase-activating protein that facilitates the conversion of active (GTP-bound) RAS to inactive (GDP-bound) RAS. Loss of *NF1* prevents such conversion and traps RAS in the active signal-transmitting stage that drives cell proliferation. Thus, the wild type *NF1* gene acts as a tumor suppressor. All other listed mechanisms also are involved in carcinogenesis, but in different tumor types.

PBD9 286,298 BP9 179 PBD8 294–295 BP8 184,189

31 A The PET scan is based upon selective uptake of a glucose derivative into tumor cells. The Warburg effect occurs when cancer cells shift their metabolism to aerobic glycolysis for selective growth advantage under harsh circumstances. Glycolysis also yields pyruvate for anabolic demands of increased tumor doublings. The *p53* and *c-MYC* genes favor this metabolic change, whereas *PTEN* inhibits tumor cell autophagy, giving cancer cells an edge in growth. Cancer cells are less differentiated than normal cells and thus have decreased ability to do many complex biochemical processes, so they favor a simple one—glycolysis. Gluconeogenesis is a function of hepatocytes in response to decreased caloric intake. The HMP shunt and Krebs cycle are more useful to normal cells maintaining themselves at the status quo. Neoplasms generate large amounts of purines from cell divisions and cell turnover that must be eliminated as uric acid, but neoplastic cells do not perform this task.

PBD9 300–301 BP9 195–196 PBD8 303–304

32 B This is an example of chromosomal translocation that brings *BCL2*, an anti-apoptosis gene, close to another gene (immunoglobulin heavy chain gene). The *BCL2* gene becomes subject to continuous stimulation by the adjacent enhancer element of the immunoglobulin gene, leading to overexpression. The *APC* gene is mutated in sporadic colon cancers and cancers associated with familial polyposis coli. The *BRCA1* gene mutation is seen in some breast cancers. The *c-MYC* gene is found on chromosome 8, and the t(8;14) translocation seen in many Burkitt lymphomas leads to *MYC* overexpression. The *IL2* mutation may be present in some T cell neoplasms. *K-RAS* mutations are present in many cancers, but not typically lymphoid malignancies.

PBD9 302–303 BP9 189–190 PBD8 296 BP8 198–199

33 A The *BCL2* gene controls production of a protein that inhibits apoptosis, and overexpression of this gene allows accumulation of abnormal cells in lymphoid tissues. Gene amplifications typically affect the *ERBB2* (*HER2*) and *MYC* oncogenes. Increased tyrosine kinase activity results from mutations affecting the *ABL* oncogene. Loss of cell cycle inhibition results from loss of tumor suppressor genes such as *p53*. Reduced DNA repair occurs in the inherited disorder xeroderma pigmentosum.

PBD9 302–303 BP9 189–190 PBD8 295–296 BP8 198–199

34 E Chromosomal telomere shortening in normal human cells limits their replicative potential and gives rise to replicative senescence. This occurs because most somatic cells lack the enzyme telomerase. Normal human stem cells do express telomerase. By contrast, 90% or more of human tumor cells show activation of telomerase, explaining continued tumor growth in the body and “immortalized” cell lines in culture. All other pathways listed cannot affect telomerase shortening, which is the rate-limiting step in indefinite replication of cells.

PBD9 303–304 BP9 190–191 PBD8 296–297 BP8 190–191

35 C Some neoplasms, including certain lymphomas, have a high proportion of cells in the replicative pool (i.e., have high growth fraction). They grow rapidly and respond rapidly to drugs that kill dividing cells. Poor vascularity would not favor rapid growth, and many neoplasms elaborate growth factors that promote vascular proliferation. Monoclonality rather than polyclonality is typical of malignant tumors, though subclones of neoplastic cells do arise over time. Aggressive neoplasms tend to be more likely to metastasize. Tumors that are highly antigenic are likely to be controlled by the immune system and not to be rapidly growing.

PBD9 303–304 BP9 190–191 PBD8 266–267 BP8 199–200

36 G Angiogenesis is a key feature of neoplasms because the growing tumor needs a blood supply, and up-regulation of factors such as VEGF and FGF help to keep the cancer growing. VEGF may be up-regulated by activation of hypoxia-inducible factor 1-alpha (HIF-1-alpha). The von Hippel-Lindau (*VHL*) gene acts as a tumor suppressor, and it normally produces a protein that binds to hypoxia-inducible factor 1-alpha so that it is cleared. *VHL* mutation leads to loss of this binding protein and activation of angiogenesis factors. Individuals with *VHL* syndrome have various neoplasms, including pheochromocytomas, renal cell carcinomas, and hemangioblastomas. The other listed genes have products that do not directly act on angiogenesis pathways.

PBD9 305–306 BP9 191–192 PBD8 297–298 BP8 200–201

37 C Several pathologic mechanisms play a role in the development of tumor metastases. The tumor cells first must become discohesive and detach from the primary site, degrade the basement membrane and interstitial connective tissue, and then attach elsewhere to become metastases. Reduced expression of adhesion molecules such as

E-cadherins promotes metastases. Tumor cells can elaborate, not reduce, proteases such as metalloproteinases to promote discohesiveness. Expression of estrogen and progesterone receptors predicts breast cancer responsiveness to antihormone therapy, and there is a monoclonal antibody, trastuzumab, that targets HER-2, a form of epidermal growth factor receptor. Tyrosine kinase receptors within cells aid in signaling cell growth.

PBD9 306–309 BP9 192–195 PBD8 301–302 BP8 203–204

38 E There is increasing evidence that localization of cancer metastases is influenced by the expression of chemokine receptors by cancer cells and elaboration of their ligands (chemokines) by certain tissues. In the case of breast cancer, the carcinoma cells express CXCR4 chemokines. Vascular, lymphatic, or basement membrane invasion is required for metastases, but these characteristics do not dictate accurately the location of metastases.

PBD9 308 BP9 194–195 PBD8 300 BP8 203–204

39 B Malignant transformation includes many genetic changes, including those rendering the malignant cells capable of invasion and metastases. CD44 plays a role in cell adhesion and enables malignant cells to metastasize. Solid tumors can express CD44 to enhance their spread to lymph nodes and other metastatic sites. Though such properties may have been present with the initial clone of malignant cells, the growth of the cancer increases the number of cells and the risk for spread. BCL2 plays a role in apoptosis. Growth factor receptor expression may make malignant cells susceptible to environmental influences, such as hormones, that drive growth. RAS gene mutations are present in many cancers and lead to loss of growth control. Vimentin is best known as a protein expressed in mesenchymal neoplasms, such as sarcomas, but it is also up-regulated in EMT.

PBD9 309 BP9 195

40 A All human nucleated cells express MHC class I antigens. CD8+ T cells recognize peptides presented by MHC class I antigens. In many tumors, especially melanomas, the tumor cells produce peptides that can be presented by MHC class I molecules. Such tumor-specific peptides are not produced by other cells, so the CD8+ T cells specific for such peptides lyse melanoma cells, but not normal melanocytes or other normal cells.

PBD9 310–311 BP9 204–205 PBD8 316–319 BP8 214–216

41 E Several types of immune cells can recognize and help destroy tumor cells. Tumor antigens that are displayed via MHC class I molecules can be recognized by cytotoxic CD8+ cells. Normal human cells should display MHC class I antigens, but many cancers do not display their antigens well, and when MHC class I molecules are not displayed, NK cells are triggered to target these cells for lysis. Macrophages may work in concert with CD8+

cells and NK cells to phagocytize and kill tumor cells when up-regulated by interferon- γ . CD4+ “helper” cells do not play a direct anticancer role. Neutrophils are ineffective against cancer cells, but may be attracted to areas of tumor necrosis. Plasma cells may produce antibodies directed against tumor antigens, but such antibodies are ineffective in controlling tumors.

PBD9 312–313 BP9 205–207 PBD8 317–318 BP8 216

42 B Primary or secondary immunodeficiency diseases carry an increased risk of neoplasia, particularly lymphomas. B cell lymphomas of the brain are 1000-fold more common in patients with AIDS from HIV infection than in the general population. Patients with diabetes mellitus can experience various vascular and infectious complications, although not neoplasia. Hypertension can lead to central nervous system hemorrhages (strokes). Multiple sclerosis is a demyelinating disease of CNS white matter and carries no significant risk of neoplasia. Tuberculosis as a chronic infection may lead to amyloidosis, not neoplasia.

PBD9 312–313 BP9 207 PBD8 319–320 BP8 217

43 B Patients with hereditary nonpolyposis colon carcinoma (HNPCC) inherit one defective copy of mismatch repair genes. Several human mismatch repair genes are involved in the development of HNPCC. Mismatch repair defects have microsatellite instability. Microsatellites are tandem repeats found throughout the genome. Normally, the length of these microsatellites remains constant. In HNPCC, these satellites are unstable and increase or decrease in length. Although HNPCC accounts for only 2% to 4% of all colon carcinomas, microsatellite instability can also be detected in about 15% of all sporadic colon carcinomas. Mutations in mismatch repair genes can be detected by the presence of microsatellite instability. The other listed options are not characteristic of HNPCC.

PBD9 314 BP9 196–197 BP8 204–205 PBD8 302

44 C These children have an autosomal recessive condition known as *xeroderma pigmentosum* (XP). Affected individuals have extreme photosensitivity, with a 2000-fold increase in the risk of skin cancers. The DNA damage is initiated by exposure to ultraviolet light; however, nucleotide excision repair cannot occur normally in XP because inheritance of one of several XP genes is abnormal. The inheritance pattern appears to be autosomal recessive, because new mutations are unlikely to occur. Inactivation of the *p53* tumor suppressor gene is found in many sporadic human cancers and in some familial cancers, but these cancers are not limited to the skin. Chromosomal translocations are often involved in the development of hematologic malignancies, although they are not often seen in skin cancers. *Aspergillus flavus*, found on moldy peanuts and other foods, produces the potent hepatic carcinogen aflatoxin B1. Human papillomavirus (HPV) is a sexually transmitted disease that is associated with the development of genital squamous cell carcinomas.

PBD9 314 BP9 197 PBD8 302 BP8 184, 204–205

45 B Approximately 5% to 10% of breast cancers are familial, and 80% of these cases result from mutations in the *BRCA1* and *BRCA2* genes. Onset of these familial cancers occurs earlier in life than the sporadic cancers. The protein products of these genes are involved in DNA repair. *BCL2* is overexpressed in some lymphoid neoplasms. The epithelial growth factor receptor *ERBB2* (*HER2*) overexpression is present in some sporadic breast cancers; other EGF alterations can be seen in lung, bladder, gastrointestinal, ovarian, and brain neoplasms. The *HST1* mutation is seen in some gastric cancers. *IL2* overexpression is associated with some T cell neoplasms. *K-RAS* overexpression is seen in many cancers, including some breast cancers, but the early age of onset and family history in this case strongly suggest *BRCA* mutations.

PBD9 315 BP9 197 PBD8 275, 303 BP8 205

46 B MicroRNAs (miRNAs) are encoded by about 5% of the human genome. miRNAs do not encode for proteins, but bind and inactivate or cleave mRNA, preventing translation of proteins by mRNA. This effectively silences gene expression without affecting the gene directly. There is abundant transfer RNA (tRNA) present in the cytoplasm that is not a rate-limiting step to translation. DNA methylation, particularly at CG dinucleotides, is a way of suppressing gene expression directly, as is seen with genomic imprinting. Mutations that occur in genes in DNA may result in reduced mRNA production or abnormal protein production, but mRNA itself is not mutated. Mitochondrial DNA (mtDNA) encodes for proteins that are mainly involved in oxidative phosphorylation metabolic pathways

PBD9 320 BP9 175 PBD8 137 BP8 205–206

47 D Chemical carcinogens can have highly reactive electrophilic groups that can directly damage DNA, leading to mutations. Direct-acting agents, such as alkylating chemotherapy drugs, do not require conversion to a carcinogen. Some environmental toxic agents, such as polycyclic hydrocarbons, require metabolic conversion to a carcinogen and are called indirect-acting agents. Phorbol esters are examples of promoters of chemical carcinogenesis that cause tumor promotion by activating protein kinase C. This enzyme phosphorylates several substrates in signal transduction pathways, including those activated by growth factors, and the cells divide. Forced cell division predisposes the accumulation of mutations in cells previously damaged by exposure to a mutagenic agent (initiator). The TGF- β pathways work via growth inhibition. Proteins such as p53 that function in DNA repair pathways can become nonfunctional through mutation. Viral infections such as hepatitis B and C tend to promote growth by binding to p53 and inactivating its protective function. Telomerase activity is not affected by carcinogens.

PBD9 322–324 BP9 199–200 PBD8 309–311 BP8 209–210

48 F Vinyl chloride is a rare cause of liver cancer. This causal relationship was easy to show, however, because hepatic angiosarcoma is a rare neoplasm. Arsenic is a risk factor for skin cancer. Asbestos exposure is linked to pleural malignant mesothelioma and to bronchogenic carcinomas in smokers. Benzene exposure is linked to leukemias. Beryllium exposure

can produce interstitial lung disease and lung cancer. Nickel exposure increases the risk of respiratory tract cancers. Exposure to naphthalene compounds is a risk factor for cancers of the urinary tract.

PBD9 323–324 BP9 199 PBD8 274 BP8 183, 209

49 D Estrogen, similar to many other hormones and drugs, by itself is not carcinogenic, but it is responsible for stimulation of endometrial growth (hyperplasia), which has a promoting effect when cellular mutations occur to produce carcinoma. Inherited susceptibility can never be completely excluded when an individual has two tumors; this can occur in patients with inherited mutations in the *p53* gene. In this case, however, there is a clear hormonal basis for the second tumor. Faulty tumor suppressor genes are not involved in hormonal promotion of a neoplasm. A paraneoplastic syndrome results from ectopic secretion of a hormone by tumor (e.g., lung cancer cells producing corticotropin). Tumor heterogeneity does not refer to two separate kinds of neoplasms; it refers to heterogeneity with a given tumor or metastasis.

PBD9 278, 324 BP9 200 PBD8 324 BP8 209

50 E Radiation is oncogenic, and the risk increases with higher dosages. Cancers of thyroid and bone as well as leukemias may develop years following environmental radiation exposure. Dosages of therapeutic radiation are carefully controlled, but risk for subsequent malignancy is still increased. The Chernobyl nuclear reactor disaster affecting persons in Belarus and Ukraine is a cautionary tale regarding environmental exposure to radiation. Trauma is not a risk factor for development of cancer, although traumatic episodes often are recalled and irrationally associated with subsequent health problems. Lack of iodine leads to goiter but not to thyroid neoplasia. Hepatocellular carcinomas can arise in cirrhosis caused by chronic alcoholism. Ataxia telangiectasia is an inherited syndrome that carries an increased risk of development of leukemias and lymphomas. Arsenic exposure, which is uncommon, leads to lung and skin cancers.

PBD9 324–325 BP9 200 PBD8 311–312 BP8 210

51 E Worldwide, increasing numbers of skin cancers occur because of sun exposure. The ultraviolet light damages the skin and damages cellular DNA, leading to mutations that can escape cellular repair mechanisms. Allergic reactions do not promote cancer. Asbestos exposure increases lung carcinoma risk in smokers and can lead to rare mesotheliomas of pleura. Chemotherapeutic agents have carcinogenic potential, particularly alkylating agents such as cyclophosphamide, but leukemias and lymphomas are the usual result. Smoking tobacco is related to many cancers, but skin cancers are not typically associated with this risk factor.

PBD9 324–325 BP9 200–201 PBD8 312 BP8 210

52 A The oncogenic potential of human papillomavirus (HPV), a sexually transmissible agent, is related to products

of two early viral genes—*E6* and *E7*. *E7* protein binds to RB protein to cause displacement of normally sequestered transcription factors, which nullifies tumor suppressor activity of the RB protein. *E6* protein binds to and inactivates the *p53* gene product. Increased epidermal growth factor receptor expression is a feature seen in many pulmonary squamous cell carcinomas, and the related *ERBB2* (*HER2*) receptor is seen in some breast carcinomas. Epigenetic modifications include DNA methylation and histone modifications which, depending on their nature, may enhance or inhibit gene expression. Inability to repair DNA damage plays a role in some colon and skin cancers. Trapping of GTP-bound RAS protein can occur in many tumors but is not related to HPV infection.

PBD9 326–327 BP9 202 PBD8 313 BP8 194, 212

53 E The largest cell population in the figure, determined to be clonal, is marking for CD4. This patient has a T cell leukemia, which develops in approximately 1% of individuals infected with human T cell lymphotropic virus type 1. Infection with Epstein-Barr virus is associated with various cancers, including Burkitt lymphoma and nasopharyngeal carcinoma. Infection with hepatitis B virus may result in hepatic cirrhosis, in which hepatocellular carcinoma may arise. HIV-1 infection causes AIDS, with a diminished CD4+ cell count. *H. pylori* promotes chronic gastritis with increased risk for gastric adenocarcinomas and B cell lymphomas.

PBD9 325–326 BP9 201 PBD8 312–313 BP8 211

54 C Although the hepatitis B virus (HBV) and hepatitis C virus (HCV) genomes do not encode for any transforming proteins, the regenerating hepatocytes are more likely to develop mutations, such as inactivation of *p53*. HBV does not have a consistent site of integration in the liver cell nuclei, and it does not contain viral oncogenes. Many DNA viruses, such as human papillomavirus (HPV), inactivate tumor suppressor genes, but there is no convincing evidence that HBV or HCV can bind to *p53* or RB proteins. Also, the HBV-encoded regulatory element, called *HBx*, disrupts normal growth of infected hepatocytes. Neither HBV nor HCV infects immune cells.

PBD9 328, 337–338 BP9 203 BP8 213 PBD8 315, 327

55 A Some chronic hepatitis B and C viral infections progress to hepatocellular and/or cholangiolar carcinoma. α -Fetoprotein (AFP) is an oncofetal protein that is a tumor marker for hepatocellular carcinomas and some testicular carcinomas. AFP is normally present in fetal life but not in adults. A serum immunoglobulin level with protein electrophoresis aids in the diagnosis of myeloma. Gastrointestinal tract adenocarcinomas, including those arising in the stomach, colon, and pancreas, as well as some lung carcinomas, may be accompanied by elevations in the serum carcinoembryonic antigen level. CA-19-9 is a tumor marker for colonic and pancreatic carcinomas. Some thyroid carcinomas produce calcitonin. Unfortunately, the sensitivity and specificity of tumor marker tests for detection of cancers, when they are small, is not high.

PBD9 328–329 BP9 203, 206, 211 PBD8 327 BP8 216, 221

56 A Cachexia is a common finding in advanced cancers, and weight loss without dieting in an adult is a “red flag” for malignancy. The exact cause for this is unknown, but increases in circulating factors such as tumor necrosis factor (TNF) may play a role. Cardiac murmurs may occur in the development of nonbacterial thrombotic endocarditis, a feature of a hypercoagulable state that may occur with advanced malignancies. Icterus is most likely to occur when there is obstruction of the biliary tract by a mass (e.g., as in pancreatic cancer), but metastases are unlikely to cause such an obstruction. Neurologic abnormalities may occur in local tumor growth impinging on nerves, but dull constant pain is the most likely abnormality in malignant neoplasms that invade nerves. Metastases to the spleen are uncommon. Tympany is uncommon in cancer because obstruction by a mass tends to be incomplete and to develop over a long time. (*Hint*: an empty beer keg is tympanitic when percussed.)

PBD9 330 BP9 208 PBD8 320–321 BP8 217–218

57 B The small cells have scant cytoplasm but marked hyperchromatism, consistent with small cell anaplastic carcinoma. This patient has Cushing syndrome resulting from ectopic corticotropin production by the tumor, a form of paraneoplastic syndrome common to small cell carcinomas of the lung. Such small cell carcinomas are of neuroendocrine derivation. A syndrome of inappropriate antidiuretic hormone (SIADH) secretion from small cell carcinomas is also common, but leads to hyponatremia as well as edema. Erythropoietin production with polycythemia is more likely to be associated with a renal cell carcinoma. Insulin and gastrin production are most often seen in islet cell tumors of the pancreas. Hypercalcemia from a parathyroid hormone-related peptide (PTHrP) is more typically associated with pulmonary squamous cell carcinomas.

PBD9 330–331 BP9 208–209 PBD8 321–322 BP8 218–219

58 E Histologic sections from malignant neoplasms are frequently assessed with a panel of immunostains to detect antigenic characteristics, such as protein expression, to aid in characterizing the cell of origin, as well as provide information in selection of treatment protocols. In this case, the immunostains are likely to reveal that this neoplasm is a high-grade urothelial carcinoma. A cytology smear shows light microscopic findings helpful to screen for malignancy, but the findings often fall short of diagnosing a specific cell type. The other listed techniques are best for determination of treatment and prognosis.

PBD9 333–335 BP9 210 PBD8 323–324 BP8 220–221

59 A The M1 designation indicates that distant metastases are present. N1 means local lymph nodes are positive for carcinoma. Elevated corticotropin levels indicate secretion of an ectopic hormone that may produce a paraneoplastic syndrome, but this is not part of staging. A T2 designation indicates that the overall size of the tumor is not large; it is still within the lung parenchyma and not impinging upon margins of the lung. The TNM system is used for staging, not microscopic grading of cellular differentiation.

PBD9 332 BP9 208–209 PBD8 322–323 BP8 218–220

60 D The rapid frozen section of resection margins helps to determine whether enough of the colon has been resected. Electron microscopy requires at least 1 day to perform, and helps to determine the cell type, but it has largely been supplanted by immunohistochemistry. Fine-needle aspiration is used for preoperative diagnosis to find a malignancy. Flow cytometry can be performed in several hours, but it is useful

mainly for prognostic information and is not a “stat” procedure. Radiologic imaging aids in preoperative diagnosis and assessment of possible metastases. Serum tumor markers may aid in preoperative diagnosis or postoperative follow-up of neoplasms.

PBD9 333 BP9 210 PBD8 323 BP8 220

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is best in each case.

1. A 54-year-old woman who has been diagnosed with early-stage breast cancer undergoes surgery for a lumpectomy to remove a small tumor detected by mammography. The pathology report confirms the early stage of the cancer and further comments on the fact that there is significant desmoplasia in the surrounding tissue. The term desmoplasia refers to

- (A) an irregular accumulation of blood vessels.
- (B) maturation and spatial arrangement of cells.
- (C) metastatic involvement of surrounding tissue.
- (D) normal tissue misplaced within another organ.
- (E) proliferation of non-neoplastic fibrous connective tissue.

2. A 24-year-old woman with a history of heavy and painful menstrual periods has been having difficulty conceiving despite months of trying to become pregnant. Further workup includes a bimanual pelvic examination and an ultrasound, which demonstrates a mass in the uterus that is presumed to be a leiomyoma. This mass is a

- (A) benign tumor of mesenchymal tissue.
- (B) benign tumor of surface epithelium.
- (C) malignant tumor of epithelial tissue.
- (D) malignant tumor of glandular epithelium.
- (E) malignant tumor of mesenchymal tissue.

3. A 68-year-old man has a long history of prostate cancer that was metastatic at the time of diagnosis. Over the past 2 months, he has had significant weight loss, loss of appetite, and loss of energy. His current

spectrum of conditions can be attributed to which of the following?

- (A) Platelet-derived growth factor
- (B) Fibroblast growth factor
- (C) Interleukin-2
- (D) Tumor necrosis factor- α
- (E) Vascular endothelial growth factor

4. A 58-year-old man with a 700-pack-per-year smoking history presents to the emergency department with shortness of breath and hemoptysis. Portable chest radiography demonstrates a large mass centrally located within the left lung field. The serum calcium is 13.0 mg/dL (normal 8.5 to 10.2). The metabolic abnormality described here is likely due to elaboration of which substance?

- (A) Adrenocorticotropic hormone-like substance
- (B) Antidiuretic hormone
- (C) Carcinoembryonic antigen
- (D) Erythropoietin
- (E) Parathyroid-related hormone

5. An 8-year-old boy is referred to the dermatologist for numerous “suspicious” pigmented lesions on the face and neck. Further history reveals that the patient has had difficulty seeing out of his right eye; he is referred to the ophthalmologist, who diagnoses an ocular melanoma. Based on the patient’s symptoms, the diagnosis of xeroderma pigmentosum is considered. This condition results from

- (A) aberrant expression of a receptor tyrosine kinase.
- (B) an inborn defect in DNA repair.
- (C) chemical carcinogenesis.
- (D) DNA viral infection.
- (E) retroviral infection.

6. A 46-year-old woman with prominent splenomegaly presents with a 3-month history of malaise, easy fatigability, weakness, weight loss, and anorexia. A complete blood count and differential demonstrates a white blood cell count of $250,000/\text{mm}^3$ (normal $3,000$ to $10,000/\text{mm}^3$) with a predominance of myelocytes, metamyelocytes, band cells, and segmented neutrophils. Cytogenetic analysis is most likely to reveal which of the following translocations?

- (A) t(8;14)
- (B) t(9;22)
- (C) t(11;22)
- (D) t(14;18)
- (E) t(15;17)

7. An 18-year-old patient presents with renal cell carcinoma. Given that this is typically a tumor of older adults, what translocation might you expect to find? This translocation is also seen in which mesenchymal malignancy?

- (A) t(X;18), synovial sarcoma
- (B) t(X;17), alveolar soft part sarcoma
- (C) t(9;22), leiomyosarcoma
- (D) t(14;18), leiomyosarcoma
- (E) t(15;17), synovial sarcoma

8. A 63-year-old woman discovers a lump in her right breast. Mammography confirms the presence of a suspicious “lump,” and a needle core biopsy is performed to determine whether the mass is malignant. The pathology report confirms that the mass is indeed cancerous and that the tissue demonstrates amplification of the *Her-2/neu* oncogene. The gene product of *Her-2/neu* is what kind of protein?

- (A) GTPase
- (B) GTPase-activating protein
- (C) Nuclear transcription factor
- (D) Receptor tyrosine kinase
- (E) A retinoic acid receptor protein

9. A 27-year-old woman has recently been diagnosed with a glioma (a malignant brain tumor). Further family history reveals that her 4-year-old son has been diagnosed with leukemia and has been undergoing chemotherapy. In addition, the patient’s mother died at 36 years of age due to metastatic breast cancer. Li-Fraumeni syndrome is suspected, given the familial clustering of this group of malignancies. The gene mutated in

Li-Fraumeni syndrome normally functions in what capacity?

- (A) Activates the GTPase activity of the gene product of the *Ras* oncogene
- (B) Excises ultraviolet light–induced thymidine dimers
- (C) Functions as a cytoplasmic tyrosine kinase
- (D) Functions as a transmembrane tyrosine kinase
- (E) Halts the cell cycle if DNA damage is detected

10. An 8-year-old child is evaluated by the pediatrician, who notes what appear to be 10 small café-au-lait spots on the child’s torso. In addition, on close inspection of the eyes, the presence of Lisch nodules is noted. The patient is diagnosed with von Recklinghausen neurofibromatosis type 1. The protein that is mutated in this disorder normally

- (A) activates the GTPase activity of *Ras*.
- (B) cleaves cellular proteins during apoptosis.
- (C) functions as a regulator of the cell cycle.
- (D) promotes angiogenesis in the growing tumor mass.
- (E) promotes the cell to undergo apoptosis.

11. A 78-year-old Navy veteran with a 600-pack-per-year history of cigarette smoking presents with cancer. During his military career, he was involved in fireproofing naval combat ships with asbestos insulation. Given his environmental exposure to both tobacco and asbestos, to which cancer do both of these carcinogens contribute?

- (A) Bladder cancer
- (B) Bronchogenic cancer
- (C) Cancer of the throat
- (D) Esophageal cancer
- (E) Mesothelioma

12. A 40-year-old woman presents with endometrial carcinoma. Her family history reveals that her mother died of endometrial cancer at age 50, while her 42-year-old brother was recently diagnosed with colon cancer. You begin to suspect a familial cancer syndrome. What gene is most likely to be mutated in this family?

- (A) *WT-1*
- (B) *APC*
- (C) *MSH2*
- (D) *p53*
- (E) *BRCA-1*

Answers and Explanations

- 1. The answer is E.** Desmoplasia refers to proliferation of non-neoplastic fibrous connective tissue within a tumor and is quite common in cases of breast cancer. An irregular accumulation of blood vessels is known as a hemangioma. An area of tissue misplaced within another organ is known as a choristoma.
- 2. The answer is A.** A leiomyoma (fibroid) is a benign tumor of the smooth muscle of the uterus and thus is an example of a benign tumor of mesenchymal origin. Profuse, painful menses and infertility are major complications of this most common tumor of the female genital tract. A leiomyosarcoma is the malignant counterpart. Malignant tumors of epithelial cells are carcinomas, and these are known as adenocarcinomas if they involve glandular epithelium. Benign tumors of surface epithelium are termed papillomas.
- 3. The answer is D.** Cachexia, or wasting due to cancer, manifests with weakness, weight loss, anorexia, anemia, and infection. The principal cytokine responsible for such changes is tumor necrosis factor- α (TNF- α). Both platelet-derived growth factor and fibroblast growth factor are involved in wound healing. Interleukin-2 (IL-2) is an immunostimulating cytokine produced by activated T cells. Vascular endothelial growth factor is important in the proliferation of blood vessels in a growing tumor.
- 4. The answer is E.** The man is likely to have a lung tumor, given his clinical presentation and the radiographic results. The patient's hypercalcemia is likely due to a paraneoplastic syndrome, such as that due to the elaboration of parathyroid-related hormone (PTHrH). PTHrH is produced by squamous cell carcinoma, whereas adrenocorticotropic-like substance and antidiuretic hormone are produced by yet another form of lung cancer—small cell carcinoma of the lung. Carcinoembryonic antigen is an oncofetal antigen produced by colon cancer cells. Erythropoietin causes secondary polycythemia and is related to renal cell carcinoma.
- 5. The answer is B.** Xeroderma pigmentosum is a hereditary DNA defect with a deficiency in the ability to repair ultraviolet (sunlight)-induced thymidine dimers. Faulty repair leads to increased sun sensitivity, with a predilection to develop skin lesions and skin cancers on exposed skin, as well as ocular melanomas. Aberrant expression of the gene for a receptor tyrosine kinase, such as the Her-2/neu gene product, can cause breast cancer. A retrovirus is responsible for the development of T-cell leukemia/lymphoma. The DNA virus human papillomavirus can cause cervical cancer.
- 6. The answer is B.** The translocation t(9;22) is the characteristic translocation associated with chronic myelogenous leukemia, forming the so-called "Philadelphia chromosome." The resultant fusion protein, p210, has increased tyrosine kinase activity that contributes to the uncontrolled proliferation in this form of leukemia. The translocation t(14;18) is seen in follicular lymphoma; t(8;14) in Burkitt lymphoma; t(15;17) in the M3 variant of acute promyelocytic leukemia (AML); and t(11;22) in Ewing sarcoma, a relatively uncommon tumor of bone.
- 7. The answer is B.** Pediatric renal cell carcinomas often demonstrate translocations involving Xp11, with t(X;17) representing the most common anomaly. This translocation is also seen in alveolar soft part sarcoma, a fact which illustrates the lack of specificity of translocations in some instances. The t(X;18) translocation is associated with synovial sarcoma, while the other translocations listed are seen in hematologic malignancies as described in the answer to question #6.
- 8. The answer is D.** Her-2/neu, also known as c-erbB2, is a receptor tyrosine kinase related to epidermal growth factor receptor and is amplified at the DNA level and overexpressed

at the protein level in some breast cancers. Ras is a GTPase that is mutated in a number of cancers. NF-1 is a GTPase-activating protein (GAP) aberrantly expressed in neurofibromatosis. An aberrant version of a retinoic acid receptor is expressed in M3 AML.

9. **The answer is E.** Li-Fraumeni syndrome is a hereditary syndrome characterized by sarcomas, breast cancer, leukemia, and brain tumors. Xeroderma pigmentosum results from a defect in repair of UV damage. Numerous transmembrane tyrosine kinases, such as Her-2/neu, are implicated in numerous cancers. *C-abl* codes for a cytoplasmic tyrosine kinase that forms a fusion protein with bcr in chronic myelogenous leukemia. NF-1, mutated in neurofibromatosis, normally activates the GTPase activity of the gene product of the *Ras* oncogene. The gene *p53*, the “guardian of the genome,” arrests the cell cycle in G1 in the event that DNA damage is detected.
10. **The answer is A.** The normal function of NF-1 is to promote the intrinsic GTPase function of the *Ras* oncogene. When the Ras protein is bound to GTP, the growth-promoting function of the molecule is “ON.” On hydrolysis of the GTP to GDP, Ras is converted to an inactive state. GAPs, such as NF-1, suppress cell growth by stimulating GTP hydrolysis. Patients with a mutation in NF-1 are susceptible to fibrosarcomas as a result of loss of function of this GAP. The molecule Bax is pro-apoptotic and antagonizes Bcl-2. Vascular endothelial growth factor promotes tumor angiogenesis. The protein p53 regulates the cell cycle if DNA damage is detected. Lastly, caspases function to cleave cellular proteins once apoptosis is triggered.
11. **The answer is B.** Tobacco contributes to the development of many cancers, including those of the bladder, lung, throat, and esophagus. Asbestos exposure carries a risk of lung cancer, as well as mesothelioma, a cancer of the pleura. Tobacco and asbestos function as cocarcinogens in the pathogenesis of lung cancer, with an approximately 50-fold greater risk of developing bronchogenic cancer of the lung than in those without such exposure.
12. **The answer is C.** This family likely has hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, or Lynch syndrome. Often, gynecologic malignancies (usually endometrial, although patients are also prone to ovarian tumors) are diagnosed before colorectal tumors in female patients with HNPCC. This syndrome is due to defects in DNA mismatch repair genes, with *MLH1*, *MSH2*, *MSH6*, and *PMS2* representing the primary culprits.

WT-1 mutations predispose patients to Wilms tumors and a variety of other defects, while *APC* is mutated in familial adenomatous polyposis (FAP). Germline mutations in *p53* are seen in Li Fraumeni syndrome, while *BRCA-1* mutations predispose women to breast carcinoma.

techniques include: DNA analysis by Southern blot, RNA analysis by northern blot, and polymerase chain reaction (PCR).

vi) DNA microarray analysis of tumours Currently, it is possible to perform molecular profiling of a tumour by use of gene chip technology which allows measurement of levels of expression of several thousand genes (up-regulation or down-regulation) simultaneously.

SELF ASSESSMENT

- Hamartoma refers to:**
 - Tumour differentiating towards more than one cell line
 - Tumour arising from totipotent cells
 - Mass of disorganised but mature cells indigenous to the part
 - Mass of ectopic rests of normal tissue
- Increased number of normal mitoses may be present in the following tissues except:**
 - Bone marrow cells
 - Nails
 - Hepatocytes
 - Intestinal epithelium
- A tumour is termed medullary when it is almost entirely composed of:**
 - Amyloid stroma
 - Large areas of necrosis
 - Abundant lymphoid tissue
 - Parenchymal cells
- All the following malignant tumours metastasise except:**
 - Synovial sarcoma
 - Malignant mesothelioma
 - Glioma
 - Neuroblastoma
- The following malignant tumours frequently spread through haematogenous route except:**
 - Bronchogenic carcinoma
 - Renal cell carcinoma
 - Follicular carcinoma thyroid
 - Seminoma testis
- Degradation of ECM is brought about by the following except:**
 - Proteases
 - Metalloproteinases
 - Free radicals
 - Cathepsin D
- Grading of tumours depends upon the following except:**
 - Degree of anaplasia
 - Metastatic spread
 - Rate of growth of cells
 - Degree of differentiation
- Patients of xeroderma pigmentosum are prone to develop the following cancers except:**
 - Basal cell carcinoma
 - Sweat gland carcinoma
 - Malignant melanoma
 - Squamous cell carcinoma
- The primary target of reactive electrophiles is as under:**
 - Cytochrome P-450
 - RNA
 - DNA
 - Mitochondria
- Carcinogenic influence of radiation appears after:**
 - < 2 years
 - 2-5 years
 - 5-10 years
 - > 10 years
- The following hereditary diseases have higher incidence of cancers due to inherited defect in DNA repair mechanism except:**
 - Ataxia telangiectasia
 - Xeroderma pigmentosum
 - Familial polyposis coli
 - Bloom's syndrome
- The following form of ionising radiation exposure is associated with highest risk of cancer:**
 - α -rays
 - β -rays
 - γ -rays
 - X-rays
- Women receiving oestrogen therapy have an increased risk of developing the following cancers except:**
 - Breast cancer
 - Endometrial carcinoma
 - Gallbladder cancer
 - Hepatocellular carcinoma

14. Important cyclins in cell cycle include the following **except**:
- A. Cyclin A
 - B. Cyclin B
 - C. Cyclin C
 - D. Cyclin D
15. Bittner milk factor is a transmissible agent belonging to the following category:
- A. Acute transforming virus
 - B. Slow transforming virus
 - C. HTLV-I
 - D. HTLV-II
16. Important examples of tumour suppressor genes implicated in human cancers include the following **except**:
- A. *RB gene*
 - B. *TP53*
 - C. *APC*
 - D. *ERB-B*
17. An example of tumour-associated antigen (TAA) is:
- A. Testis specific antigen (MAGE)
 - B. Alpha-fetoprotein (AFP)
 - C. Carcinoembryonic antigen (CEA)
 - D. Prostate specific antigen (PSA)
18. Hypercalcaemia as a paraneoplastic syndrome is observed in the following tumours **except**:
- A. Squamous cell carcinoma lung
 - B. Small cell carcinoma lung
 - C. Renal cell carcinoma
 - D. Breast cancer
19. Lymphocytic infiltrate is frequently present in the following tumours indicative of host immune response **except**:
- A. Seminoma testis
 - B. Medullary carcinoma breast
 - C. Papillary carcinoma thyroid
 - D. Malignant melanoma
20. The following antibody-stain is used in immunohistochemistry to identify epithelial cells:
- A. Desmin
 - B. Vimentin
 - C. Cytokeratin
 - D. Neurofilaments
21. Which of the following viral infection is not known to produce any human tumour?
- A. Polyoma virus
 - B. EBV
 - C. HSV
 - D. HTLV
22. All are autosomal dominant inherited cancer syndromes **except**:
- A. Retinoblastoma
 - B. Xeroderma pigmentosum
 - C. HNPCC
 - D. Neurofibromatosis
23. Phosphorylation of retinoblastoma gene:
- A. Inhibits cell replication
 - B. Promotes cellular quiescence
 - C. Stops cell cycle progression
 - D. Promotes cell division
24. p53:
- A. Activates cyclins
 - B. Activates BAX
 - C. Activates CDKs
 - D. Activates bcl2
25. All are matrix metalloproteinases **except**:
- A. Collagenase
 - B. Gelatinase
 - C. Stromelysin
 - D. Elastase
26. All are anti-angiogenesis factors **except**:
- A. Thrombospondin-1
 - B. Basic fibroblast growth factor (bFGF)
 - C. Endostatin
 - D. Angiostatin
27. Which of the following is a test for mutagenicity?
- A. Kveim's test
 - B. Ame's test
 - C. Schilling's test
 - D. Mantoux test

28. All are autosomal dominant inherited cancer syndromes **except**:
- A. Retinoblastoma B. Xeroderma pigmentosum
C. HNPCC D. Neurofibromatosis
29. DNA extraction is a pre-requisite for the following molecular techniques **except**:
- A. PCR technique B. In situ hybridisation
C. Western blot technique D. Southern blot technique
30. All are methods of cell proliferation analysis **except**:
- A. Microspectrophotometry B. Flow cytometry
C. PCR D. Immunohistochemistry

KEY

1 = C	2 = B	3 = D	4 = C	5 = D
6 = C	7 = B	8 = B	9 = C	10 = D
11 = C	12 = A	13 = C	14 = C	15 = B
16 = D	17 = D	18 = B	19 = C	20 = C
21 = A	22 = B	23 = D	24 = B	25 = D
26 = B	27 = B	28 = B	29 = B	30 = C

