The Cell Cycle

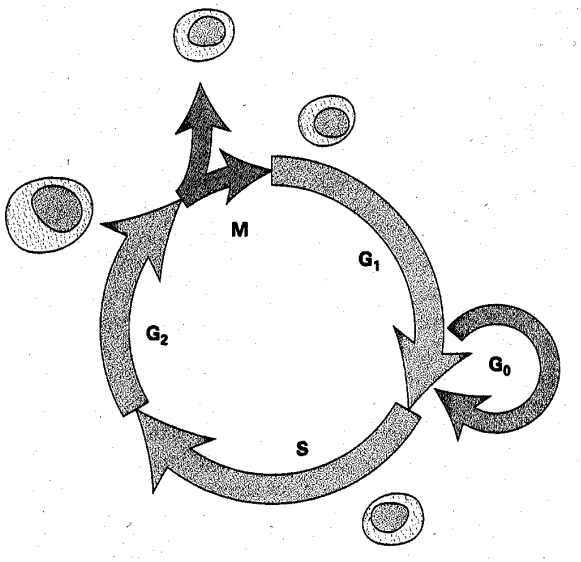
- New cells arise when one cell divides or two cells (like sperm and egg) fuse.
- These events initiate a cell-replication program that is encoded in the DNA and executed by proteins.
- A period of cell growth, and replication of DNA is then followed by cell division.
- Cell growth and division is highly regulated in the body.
- Cancer occurs when a cell escapes from this regulation and growth is unchecked.

Most eukaryotic cells live according to an internal clock, they proceed through a series of phases called the **cell cycle**.

- **G_1**: the **g**ap between the end of mitosis and beginning of S phase
- **S phase**: DNA is duplicated: cells have a DNA content that progressively increases from 2n to 4n.
- **G_2**: time between the end of S and the beginning of mitosis
- **M**- mitosis: Cell division: the two daughter cells receive all of the genetic information of the parent cell.
- **G_0:** quiescent cells, not actively cycling.

G1 and G2 are periods of apparent inactivity between the major discernable events in the cell cycle.

- Bacteria can replicate their single chromosome and divide in about 20 minutes.
- Most mammalian cells have a cell cycle time on the order of 10-12 hours.
- Some cells (nerve cells, striated muscle cells) do not divide at all. They have temporarily exited from the cell cycle and entered a quiescent state called G_0.



Checkpoints

“Proofreading before division”

Progress through the cell cycle is regulated at key **checkpoints** along the way that monitor the status of the cell.

Before entering mitosis, the integrity of the DNA is checked.

Exposure to radiation causes a block in G_2.

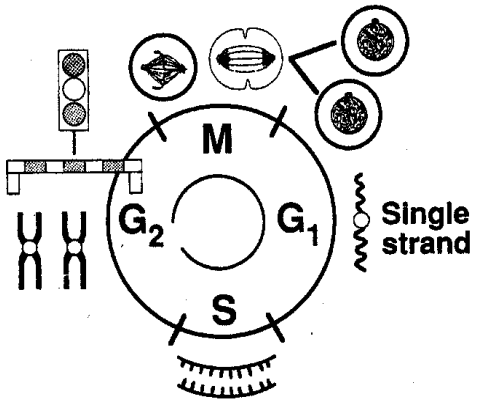
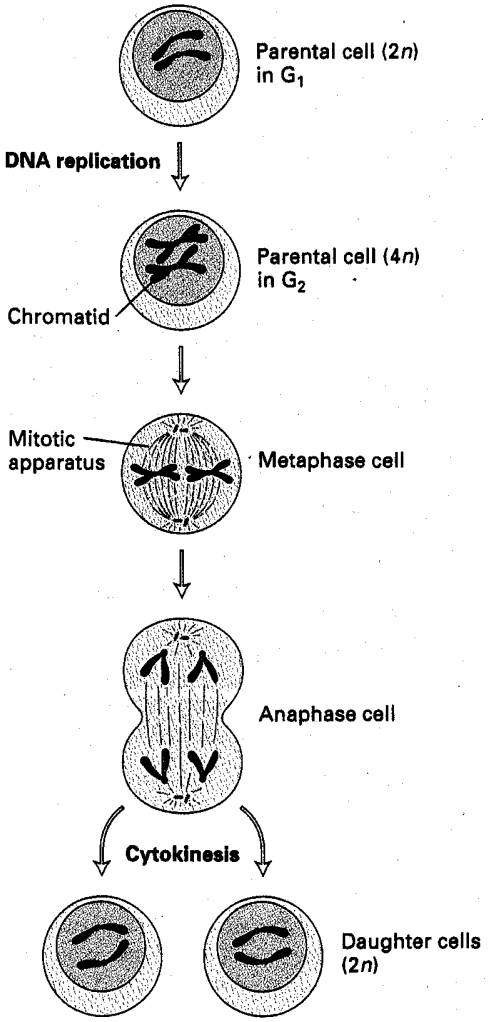


Figure 4.11. Diagram illustrating the site of action and function of the molecular checkpoint gene. Cells exposed to any DNA-damaging agent, including ionizing radiation, are arrested in G_2 phase. The function of the pause in cell-cycle progression is to allow a check of chromosome integrity before the complex task of mitosis is attempted. Cells in which the checkpoint gene is inactivated are much more sensitive to killing by γ-rays or ultraviolet light. The mutant gene isolated from a sensitive strain of yeast functions as a checkpoint gene.



[Lodish, 2000]

Mitosis is the process for partitioning the genome equally during cell division. The **mitotic apparatus** captures the chromosomes and pulls them to the opposite sides of the dividing cell.

- **Prophase**: the replicated chromosomes (each containing two identical chromatids) are condensed and released to the cytoplasm when the nuclear membrane breaks down.
- **Metaphase** and **anaphase:** the chromosomes are sorted and moved to opposite ends of the cell.
- **Telophase**: marks the end of mitosis as a membrane is reformed around each set of chromosomes.
- **Cytokinesis**: division of the cytoplasm and separation of the two daughter cells.

What’s cancer?

Cancer-uncontrolled cell growth

- **Tumor**- mass formed by growing cancer cells
- **Malignant**- destructive, invasive, can metastasize
- **Benign**- slowly growing, does not invade surrounding tissues or metastasize, usually encapsulated.
- **Metastasis**- spread of the tumor cells to other sites, where they establish secondary areas of growth.
- **Angiogenesis**- both primary and secondary tumors require new blood vessels to sustain growth.

E.g.,

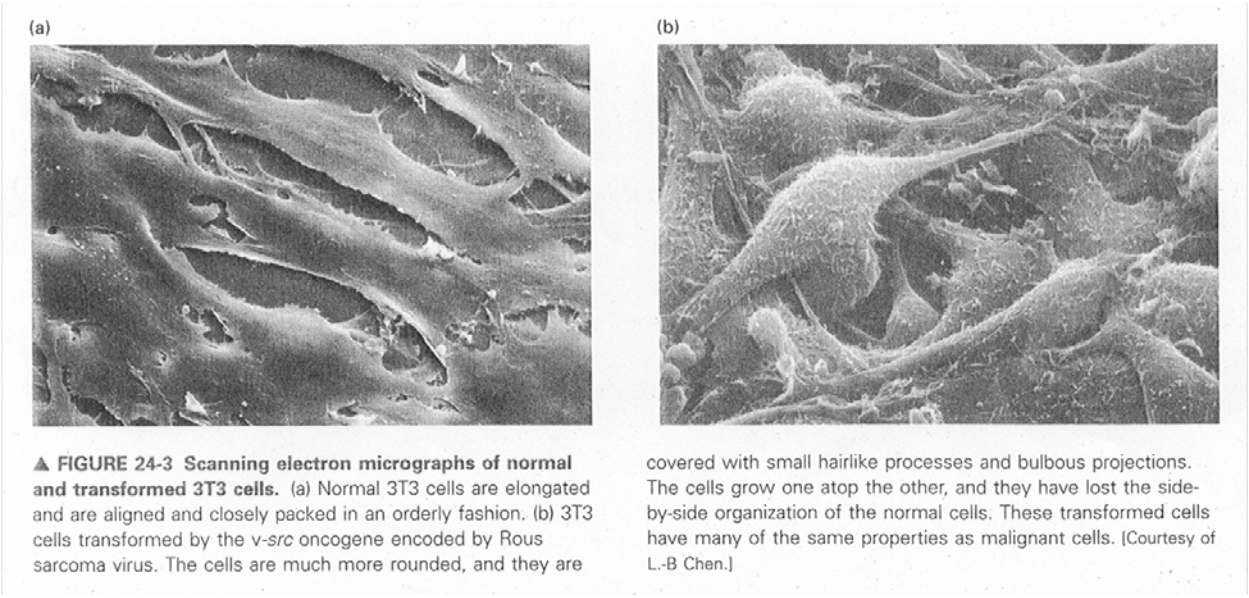
- **Carcinoma**- solid tumor arising from epithelial tissue such as skin, colon, lung, breast.
- **Sarcoma**- solid tumor arising from connective tissue such as bone.

Tumor	Tissue
Malignant	
Adenocarcinoma	**Glandular**
Carcinoma	Epithelial
Glioma	Glial cells in CNS
Hepatoma	Liver
Leukemia	WBCs leukocytes
Lymphoma	lymphocytes
Melanoma	Pigment cells
Myeloma	Plasma cells (bone marrow)
Nephroblastoma	Kidney
Neuroblastoma	Nerve cells
Retinoblastoma	Eye (retina)
Sarcoma	Connective tissue
Seminoma	Reproductive cells
Squamous	Epidermal
Usually benign	
Adenoma	Glandular
Chondroma	Cartilage
Fibroma	Fibroblasts
Osteoma	Bone
papilloma	Surface epithelia

Cancer cells can multiply in the absence of normally required growth factors and are resistant to signals that normally program cell death.

Malignant cells show many differences from normal counterparts.

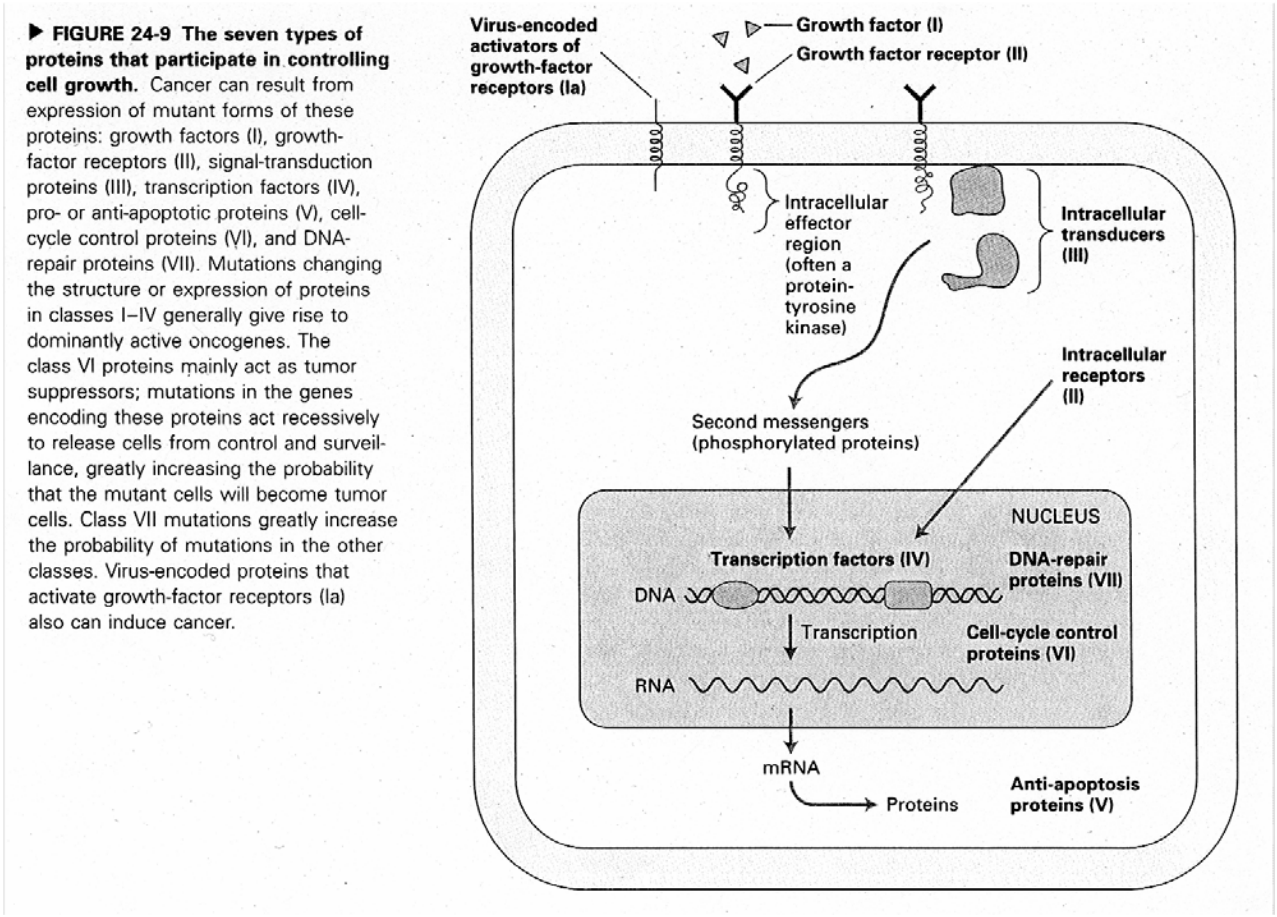
- Less well differentiated
- More rapid growth
- Loss of normal attachments to neighbors, loss of contact inhibition
- Growth factor independent cell growth
- Genetically unstable (phenotype and genotype can change with time)
- Disruptions to cytoskeleton
- Higher metabolic rate
- Changes in cytoplasmic ion concentrations



▲ **FIGURE 24-3 Scanning electron micrographs of normal and transformed 3T3 cells.** (a) Normal 3T3 cells are elongated and are aligned and closely packed in an orderly fashion. (b) 3T3 cells transformed by the v-*src* oncogene encoded by Rous sarcoma virus. The cells are much more rounded, and they are covered with small hairlike processes and bulbous projections. The cells grow one atop the other, and they have lost the side-by-side organization of the normal cells. These transformed cells have many of the same properties as malignant cells. [Courtesy of L.-B Chen.]

Genes involved in cancer

Seven types of proteins participate in the control of cell growth.



▶ **FIGURE 24-9 The seven types of proteins that participate in controlling cell growth.** Cancer can result from expression of mutant forms of these proteins: growth factors (I), growth-factor receptors (II), signal-transduction proteins (III), transcription factors (IV), pro- or anti-apoptotic proteins (V), cell-cycle control proteins (VI), and DNA-repair proteins (VII). Mutations changing the structure or expression of proteins in classes I–IV generally give rise to dominantly active oncogenes. The class VI proteins mainly act as tumor suppressors; mutations in the genes encoding these proteins act recessively to release cells from control and surveillance, greatly increasing the probability that the mutant cells will become tumor cells. Class VII mutations greatly increase the probability of mutations in the other classes. Virus-encoded proteins that activate growth-factor receptors (Ia) also can induce cancer.

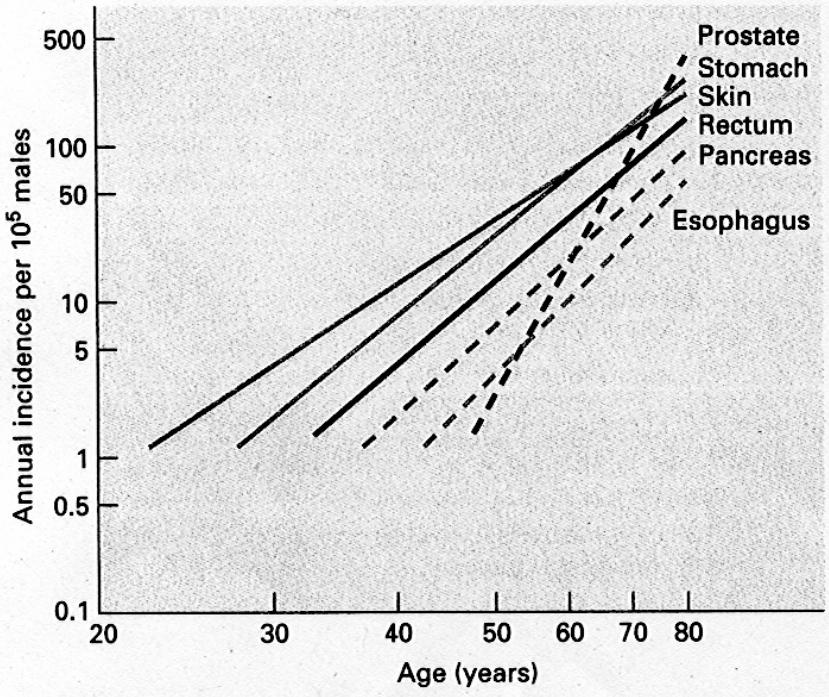
Oncogenes- cancer causing genes
Many oncogenes are altered forms of normal cellular genes called proto-oncogenes
Gain-of-function mutations convert proto-oncogenes into oncogenes.

Tumor suppressor genes- genes which code for cell cycle control proteins

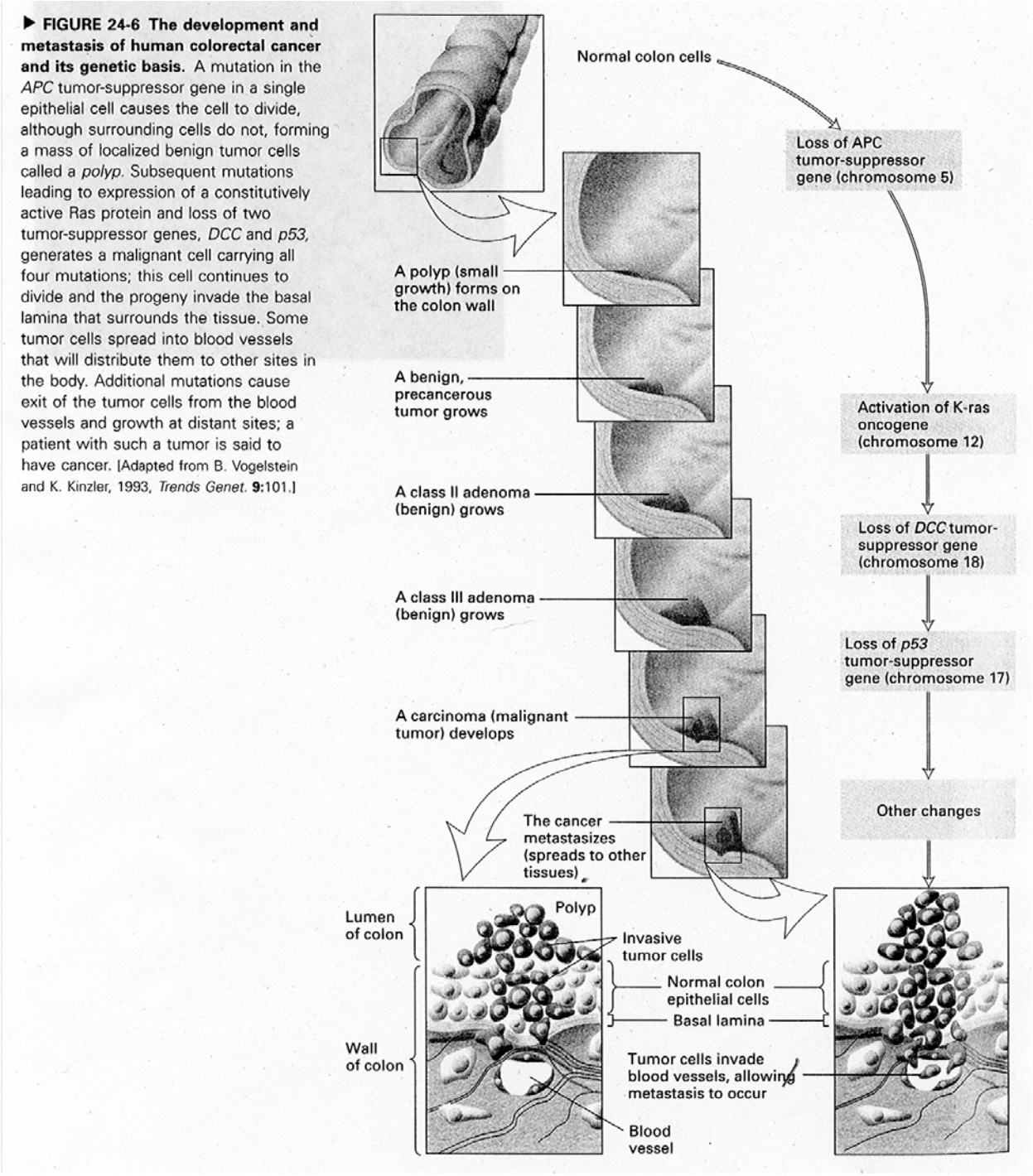
- Loss-of-function mutations in tumor suppressor genes are oncogenic.
- Usually act recessively, both copies must be deleted or mutated to lose the normal cell growth suppression effect.

Multi-step progression of cancer

Development of cancer requires several mutations
Consistent with the observation of increased incidence as a function of age



▲ FIGURE 24-5 The incidence of several human cancers increases markedly with age. Note that the logarithm of annual incidence is plotted versus the logarithm of age. [From B. Vogelstein and K. Kinzler, 1993, *Trends Genet.* **9**:101.]



▶ **FIGURE 24-6 The development and metastasis of human colorectal cancer and its genetic basis.** A mutation in the *APC* tumor-suppressor gene in a single epithelial cell causes the cell to divide, although surrounding cells do not, forming a mass of localized benign tumor cells called a *polyp.* Subsequent mutations leading to expression of a constitutively active Ras protein and loss of two tumor-suppressor genes, *DCC* and *p53,* generates a malignant cell carrying all four mutations; this cell continues to divide and the progeny invade the basal lamina that surrounds the tissue. Some tumor cells spread into blood vessels that will distribute them to other sites in the body. Additional mutations cause exit of the tumor cells from the blood vessels and growth at distant sites; a patient with such a tumor is said to have cancer. [Adapted from B. Vogelstein and K. Kinzler, 1993, *Trends Genet.* **9**:101.]

- Cancer: a clone from a single cell?
- Colorectal carcinoma well studied with biopsy material and genetic analysis at all stages of development.
    - Visible on endoscopy
    - Biopsy material available
    - Analyze genetic mutations

Carcinogens- agents that can cause cancer

Viruses- can introduce oncogenes, or suppress genes that inhibit cell growth

- **Retroviruses**- RNA viruses, integrate into the genome of the infected cell as a DNA copy and can carry oncogenes derived from cellular proto-oncogenes.

- **DNA tumor viruses**- contain oncogenes of purely viral origin

Chemicals- usually thought to act as carcinogens by causing DNA damage.

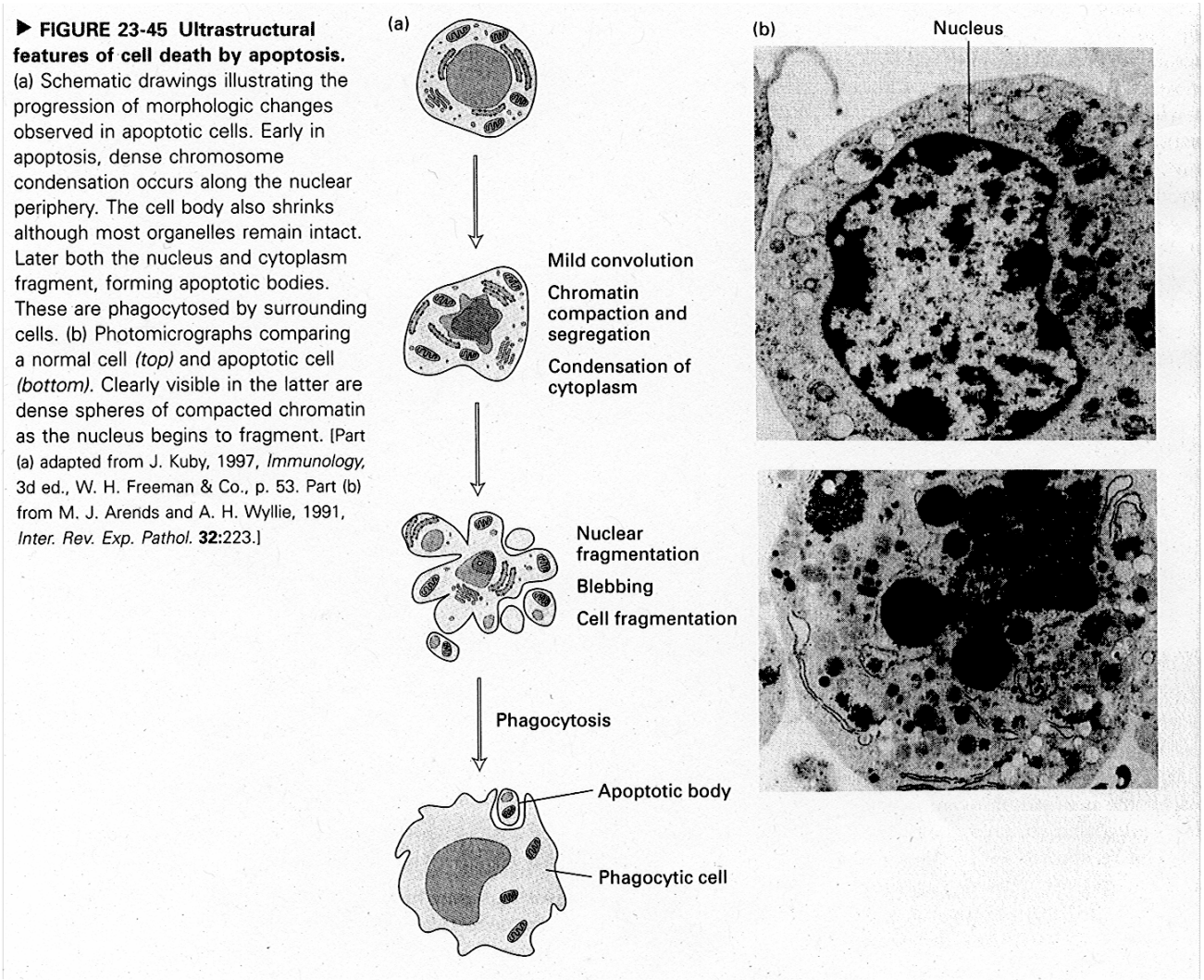
- Some of the most potent are alkylating agents that are capable of adding organic groups to DNA.
- Others, (polycyclic hydrocarbons) become carcinogenic when they are biochemically modified in cells, often as the cell attempts detoxification
- Phorbol esters- do not cause DNA damage, but promote growth (may only work when DNA damage also occurs from another agent)

Radiation- also thought to act by causing DNA danage

- **UV**- is absorbed directly by DNA, causing base changes, in sunlight can lead to skin cancer.
- **Ionizing radiation** is actually a relatively weak carcinogen.

Apoptosis- now recognized that cancer is due not only to uncontrolled cell growth, but also to loss of control in regulated cell growth.

In an adult, normal tissues are in homeostasis- no net increase in cell numbers because of a balance between cell division and cell death due to apoptosis.



▶ **FIGURE 23-45 Ultrastructural features of cell death by apoptosis.** (a) Schematic drawings illustrating the progression of morphologic changes observed in apoptotic cells. Early in apoptosis, dense chromosome condensation occurs along the nuclear periphery. The cell body also shrinks although most organelles remain intact. Later both the nucleus and cytoplasm fragment, forming apoptotic bodies. These are phagocytosed by surrounding cells. (b) Photomicrographs comparing a normal cell *(top)* and apoptotic cell *(bottom)*. Clearly visible in the latter are dense spheres of compacted chromatin as the nucleus begins to fragment. [Part (a) adapted from J. Kuby, 1997, *Immunology,* 3d ed., W. H. Freeman & Co., p. 53. Part (b) from M. J. Arends and A. H. Wyllie, 1991, *Inter. Rev. Exp. Pathol.* **32:**223.]

Apoptosis vs. Necrosis