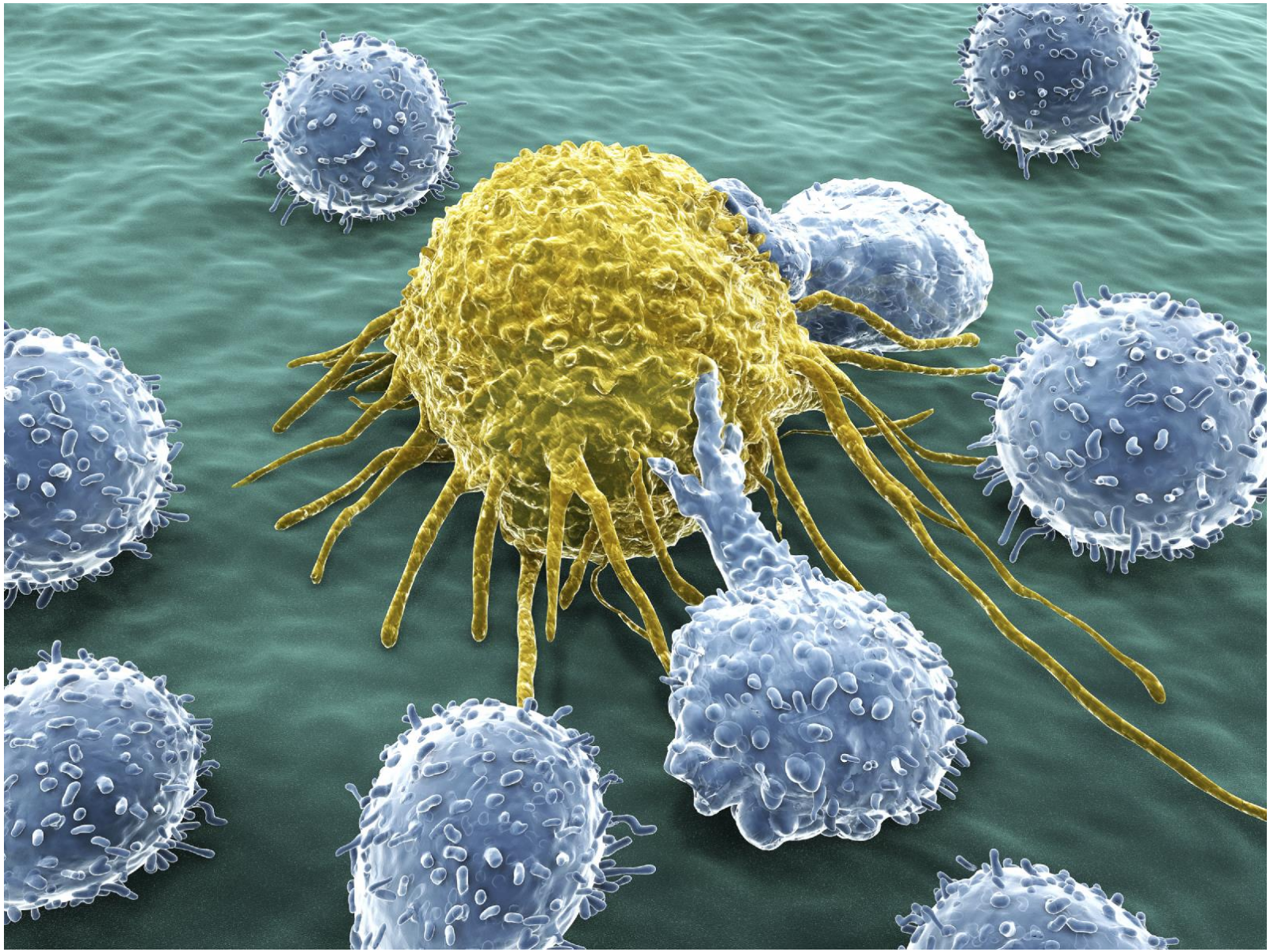
Molecular Biology of Cancer



- Cancer cells break the most basic rules of cell behavior by which multicellular organisms are built and maintained, and they exploit every kind of opportunity to do so.

- In studying these transgressions, we discover what the normal rules are and how they are enforced.

- Thus, in the context of cell biology, cancer has a unique importance, and the emphasis given to cancer research has profoundly benefited a much wider area of biomedical science than that of cancer alone.

- The body of an animal operates as a society or ecosystem.

- The individual members are cells that reproduce by cell division and organize into collaborative assemblies called tissues.

- This society is very peculiar, however, because selfsacrifice—as opposed to survival of the fittest—is the rule.

- Ultimately, all of the somatic cell lineages in animals are committed to die: they leave no progeny and instead dedicate their existence to support of the germ cells, which alone have a chance of continued survival.

- There is no particular mystery in this, for the body is a clone derived from a fertilized egg, and the genome of the somatic cells is the same as that of the germ cell lineage that gives rise to sperm or eggs.

- By their self-sacrifice for the sake of the germ cells, the somatic cells help to propagate copies of their own genes.

- Thus, unlike free-living cells such as bacteria, which compete to survive, the cells of a multicellular organism are committed to collaboration.

- To coordinate their behavior, the cells send, receive, and interpret an elaborate set of extracellular signals that serve as social controls, directing each of them how to act.

- As a result, each cell behaves in a socially responsible manner—resting, growing, dividing, differentiating, or dying—as needed for the good of the organism.

- Molecular disturbances that upset this harmony mean trouble for a multicellular society.

- In a human body with more than 10^{14} cells, billions of cells experience mutations every day, potentially disrupting the social controls.

- Most dangerously, a mutation may give one cell a selective advantage, allowing it to grow and divide more vigorously and survive more readily than its neighbors and to become a founder of a growing mutant clone.

- A mutation that promotes such selfish behavior by individual members of the cooperative can jeopardize the future of the whole enterprise.

- Over time, repeated rounds of mutation, competition, and natural selection operating within the population of somatic cells can cause matters to go from bad to worse.

- These are the basic ingredients of cancer: it is a disease in which an individual mutant clone of cells begins by prospering at the expense of its neighbors, but in the end the descendants of this clone can destroy the whole cellular society.

- Cancer cells are defined by two heritable properties: (1) they reproduce in defiance of the normal restraints on cell growth and division, and (2) they invade and colonize territories normally reserved for other cells.

- It is the combination of these properties that makes cancers particularly dangerous.

- An abnormal cell that grows (increases in mass) and proliferates (divides) out of control will give rise to a tumor, or neoplasm—literally, a new growth.

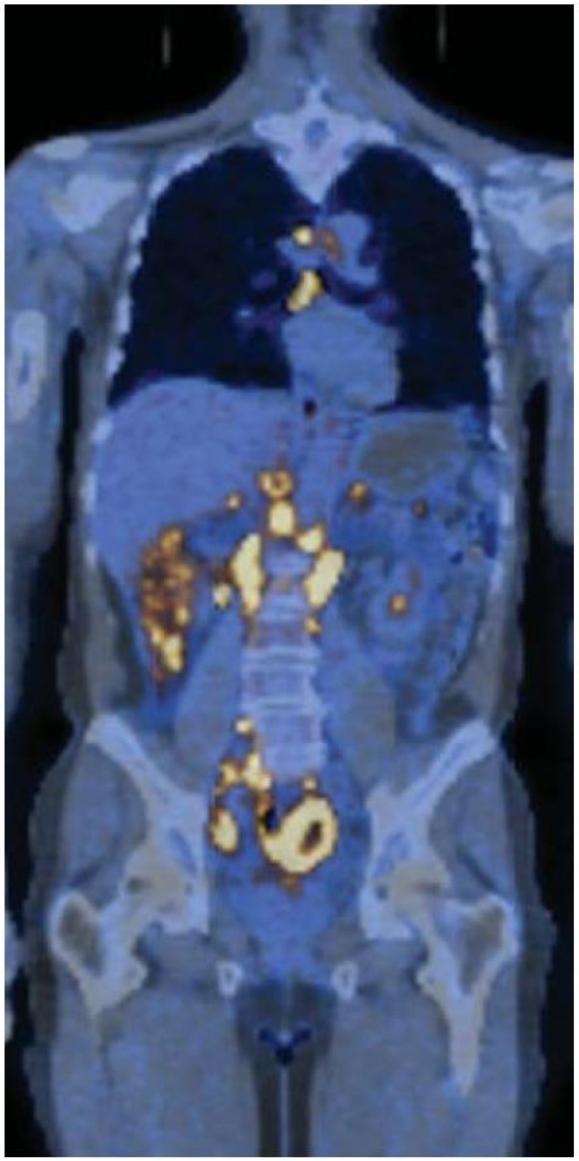
- As long as the neoplastic cells do not become invasive, however, the tumor is said to be benign, and removing or destroying the mass locally usually achieves a complete cure.

- A tumor is considered a cancer only if it is malignant, that is, only if its cells have acquired the ability to invade surrounding tissue.

- Invasiveness is an essential characteristic of cancer cells.

- It allows them to break loose, enter blood or lymphatic vessels, and form secondary tumors, called metastases, at other sites in the body.

- The more widely a cancer spreads, the harder it becomes to eradicate, and it is generally metastases that kill the cancer patient.



- Malignant tumors typically give rise to metastases, making the cancer hard to eradicate.
- Shown in this fusion image is a whole-body scan of a patient with metastatic non-Hodgkins lymphoma (NHL).
- The background image of the body's tissues was obtained by CT (computed X-ray tomography) scanning. Overlaid on this image, a PET (positron emission tomography) scan that detects the uptake of radioactively labeled fluoro-deoxyglucose (FDG) in various tissues reveals the tumor tissue (yellow).
- High FDG uptake indicates cells with unusually active glucose uptake and metabolism, a characteristic of tumors. The yellow spots in the abdominal region reveal multiple NHL metastases.

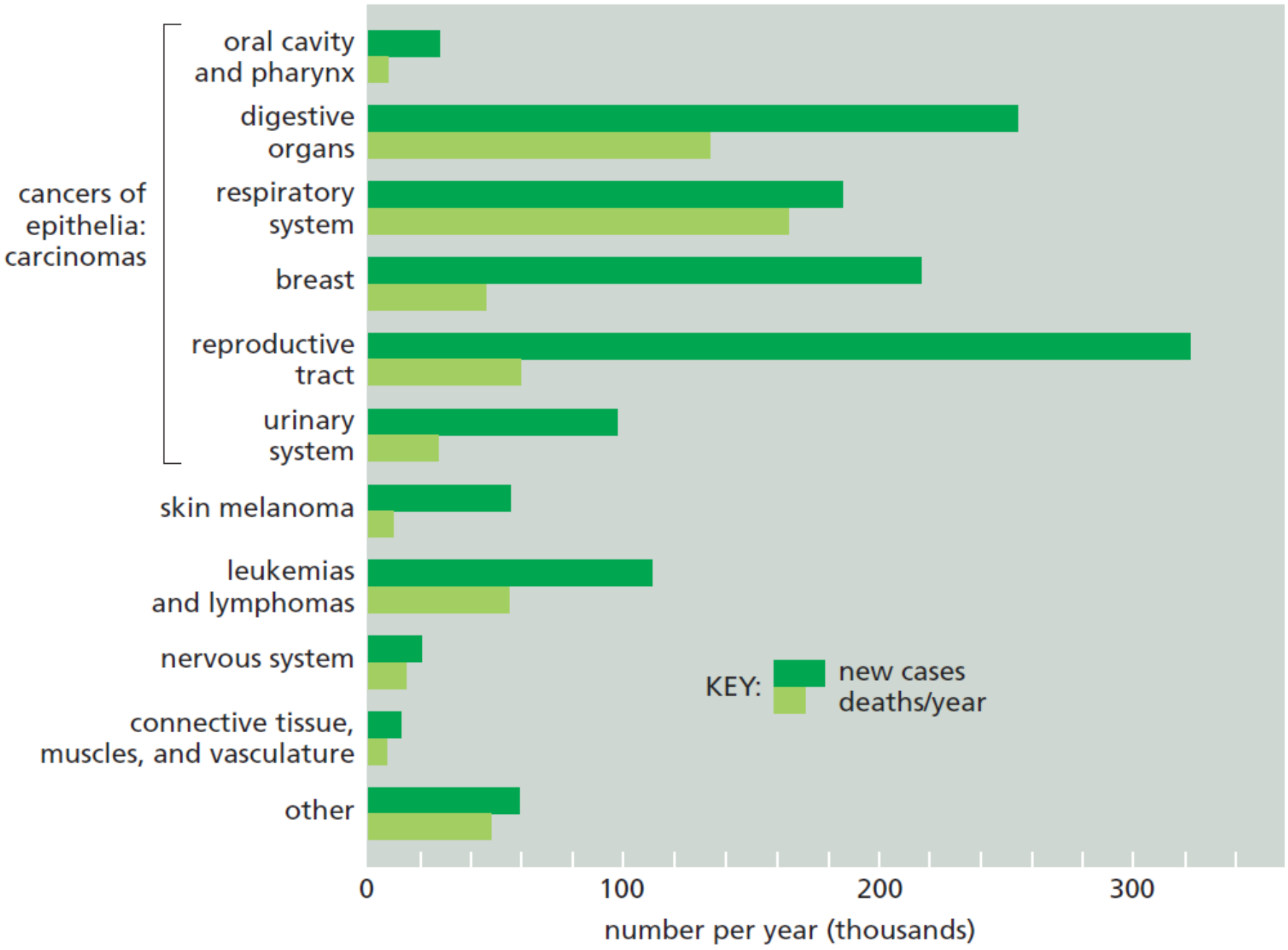
- Cancers are classified according to the tissue and cell type from which they arise.

- Carcinomas are cancers arising from epithelial cells, and they are by far the most common cancers in humans.

- Sarcomas arise from connective tissue or muscle cells.

- Cancers that do not fit in either of these two broad categories include the various leukemias and lymphomas, derived from white blood cells and their precursors (hemopoietic cells), as well as cancers derived from cells of the nervous system.

- Each broad category has many subdivisions according to the specific cell type, location in the body, and the microscopic appearance of the tumor.


cancers of epithelia: carcinomas
oral cavity and pharynx
digestive organs
respiratory system
breast
reproductive tract
urinary system
skin melanoma
leukemias and lymphomas
nervous system
connective tissue, muscles, and vasculature
other
KEY:
new cases
deaths/year
0
100
200
300
number per year (thousands)

- In parallel with the set of names for malignant tumors, there is a related set of names for benign tumors: an adenoma, for example, is a benign epithelial tumor with a glandular organization; the corresponding type of malignant tumor is an adenocarcinoma.

- Similarly a chondroma and a chondrosarcoma are, respectively, benign and malignant tumors of cartilage.

- Most cancers have characteristics that reflect their origin.

- Thus, for example, the cells of a basal-cell carcinoma, derived from a keratinocyte stem cell in the skin, generally continue to synthesize cytokeratin intermediate filaments, whereas the cells of a melanoma, derived from a pigment cell in the skin, will often (but not always) continue to make pigment granules.

- Cancers originating from different cell types are, in general, very different diseases.

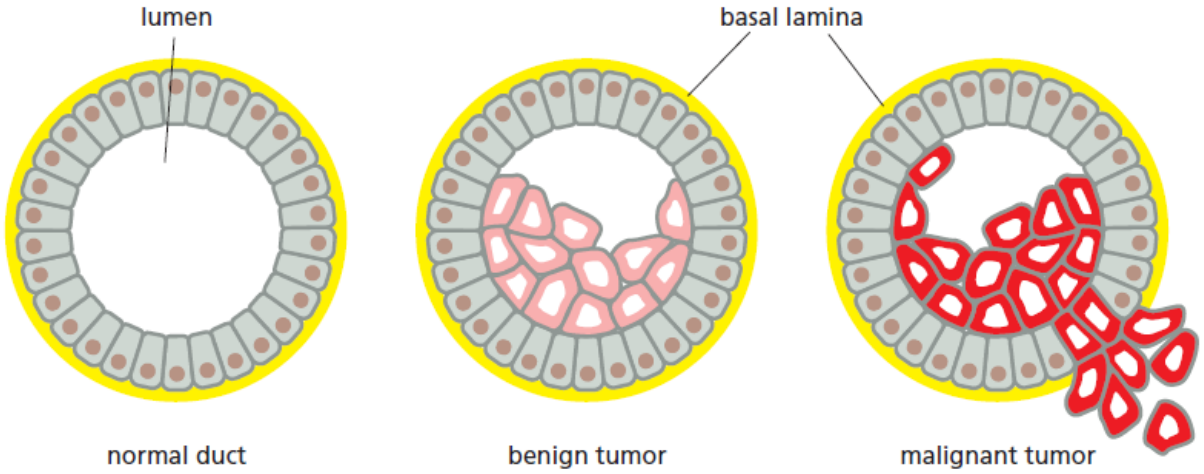


Figure 20–3 Benign versus malignant tumors. A benign glandular tumor (an adenoma) remains inside the basal lamina that marks the boundary of the normal structure (a duct, in this example), whereas a malignant glandular tumor (an adenocarcinoma) destroys duct integrity as shown. There are many forms that such tumors may take.

- Basal-cell carcinomas of the skin, for example, are only locally invasive and rarely metastasize, whereas melanomas can become much more malignant and often form metastases.

- Basal-cell carcinomas are readily cured by surgery or local irradiation, whereas malignant melanomas, once they have metastasized widely, are usually fatal.

- About 80% of human cancers are carcinomas, perhaps because most of the cell proliferation in adults occurs in epithelia or because epithelial tissues are most frequently exposed to the various forms of physical and chemical damage that favor the development of cancer.

- Even when a cancer has metastasized, we can usually trace its origins to a single primary tumor, arising in a specific organ.

- The primary tumor is thought to derive by cell division from a single cell that initially experienced some heritable change.

- Subsequently, additional changes accumulate in some of the descendants of this cell, allowing them to outgrow, out-divide, and often outlive their neighbors.

- By the time it is first detected, a typical human cancer will have been developing for many years and will already contain about a billion cancer cells or more.

- Tumors will usually also contain a variety of other cell types—fibroblasts, for example, in the supporting connective tissue associated with a carcinoma, as well as inflammatory cells.

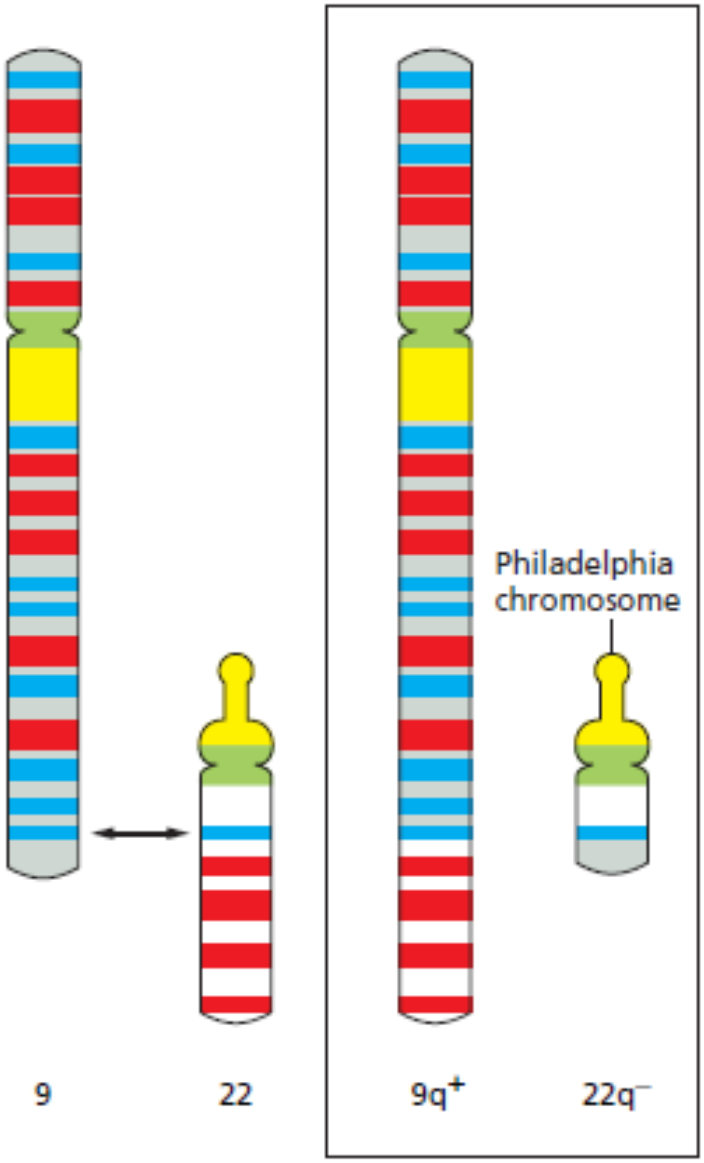
- Even when a cancer has metastasized, we can usually trace its origins to a single primary tumor, arising in a specific organ.

- The primary tumor is thought to derive by cell division from a single cell that initially experienced some heritable change.

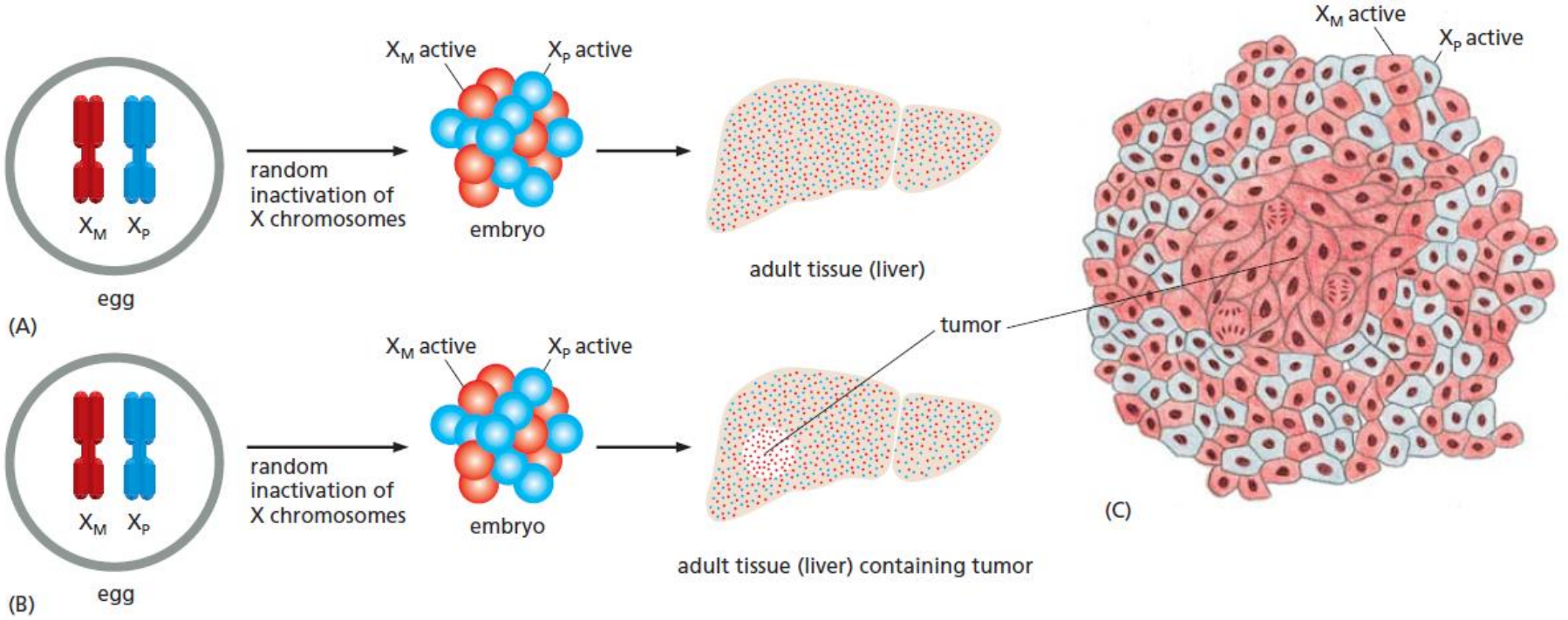
- Subsequently, additional changes accumulate in some of the descendants of this cell, allowing them to outgrow, out-divide, and often outlive their neighbors.

- By the time it is first detected, a typical human cancer will have been developing for many years and will already contain about a billion cancer cells or more.

- Tumors will usually also contain a variety of other cell types—fibroblasts, for example, in the supporting connective tissue associated with a carcinoma, as well as inflammatory cells.



- How can we be sure that the cancer cells are a clone descended from a single abnormal cell?
- Molecular analyses of chromosomes in tumor cells clearly demonstrate the clonal origin of those cells.
- In almost all patients with chronic myelogenous leukemia (CML), for example, we can distinguish leukemic white blood cells from normal cells by a specific chromosomal abnormality: the so-called Philadelphia chromosome, created by a translocation between the long arms of chromosomes 9 and 22.
- Many other lines of evidence, from a variety of cancers, point to the same conclusion: most cancers originate from a single aberrant cell



- Evidence from X-inactivation mosaics that demonstrates the monoclonal origin of cancers. (A) As a result of a random process that occurs in the early embryo, practically every normal tissue in a woman's body is a mixture of cells with different X chromosomes heritably inactivated (indicated here by the mixture of red cells and blue cells in the normal tissue).

- (B) When the cells of a cancer are tested for their expression of an X-linked marker gene (a specific form of the enzyme G6PD), however, they are usually all found to have the same X chromosome inactivated, as shown in (C). This implies that they are all derived from a single cancerous founder cell.

- If a single abnormal cell is to give rise to a tumor, it must pass on its abnormality to its progeny: the aberration has to be heritable.

- The cells of many cancers can be shown to have one or more shared detectable abnormalities in their DNA sequence that distinguish them from the normal cells surrounding the tumor.

- This agrees with the finding that many of the agents that provoke the development of cancer also cause genetic changes.

- Thus, carcinogenesis (the generation of cancer) appears to be linked to mutagenesis (the production of a change in the DNA sequence).

- This correlation is particularly clear for two classes of agents: (1) chemical carcinogens (whichtypically cause simple local changes in the nucleotide sequence), and (2) radiation such as x-rays (which typically cause chromosome breaks and translocations) or UV light (which causes specific DNA base alterations).

- The conclusion that the development of cancer depends on somatic mutations is further supported by the finding that people who have inherited a genetic defect in one of several DNA repair mechanisms, causing their cells to accumulate mutations at an elevated rate, show a strong predisposition to develop cancer.

- People with the disease xeroderma pigmentosum, for example, have defects in the system that repairs DNA damage induced by UV light, and they have a greatly increased incidence of skin cancers.

- Likewise, mice lacking specific DNA repair genes are abnormally prone to cancer.

- An estimated 10^{16} cell divisions occur in a normal human body in the course of a typical lifetime.

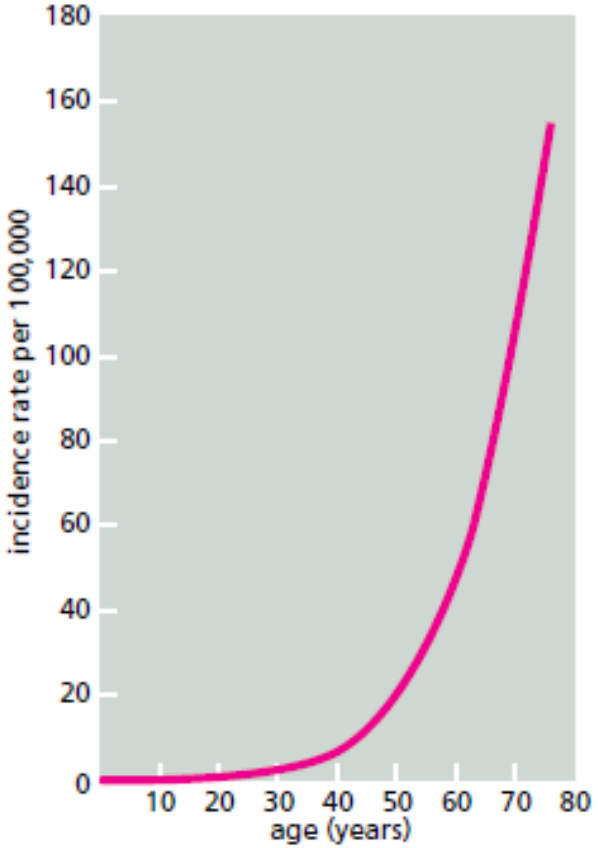
- Even in an environment that is free of mutagens, mutations would occur spontaneously at an estimated rate of about 10^{-6} mutations per gene per cell division—a value set by fundamental limitations on the accuracy of DNA replication and repair.

- Thus, in a typical lifetime, every single gene is likely to have undergone mutation on about 10^{10} separate occasions in a human.

- From this point of view, the problem of cancer seems to be not why it occurs, but why it occurs so infrequently.

- Clearly, if a single mutation were enough to convert a typical healthy cell into a cancer cell that proliferates without restraint, we would not be viable organisms.

- Many lines of evidence indicate that the development of a cancer typically requires that a substantial number of independent, rare genetic accidents occur in the lineage of one cell.



- The chance of developing cancer in any given year of life is dependent of age, cancer is caused by a progressive accumulation of random mutations in a single lineage of cells.
- For those cancers known to have a specific external cause, the disease does not usually become apparent until long after exposure to the causal agent.
- The incidence of lung cancer, for example, does not begin to rise steeply until after 20 years of heavy smoking.
- Similarly, the incidence of leukemias in Hiroshima and Nagasaki did not show a marked rise until about 5 years after the explosion of the atomic bombs, and industrial workers exposed for a limited period to chemical carcinogens do not usually develop the cancers characteristic of their occupation until 10, 20, or even more years after the exposure

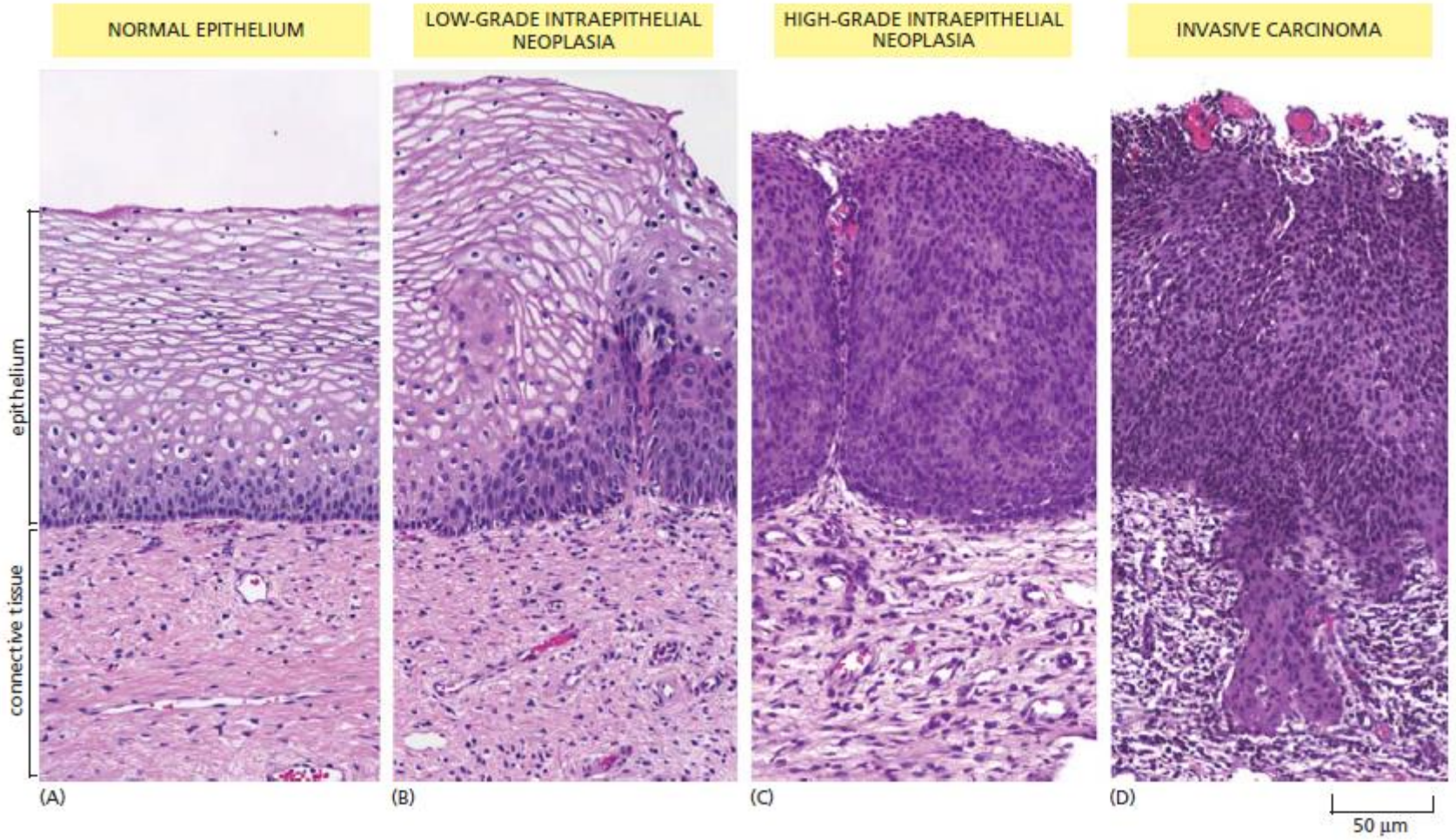
- The concept that the development of a cancer requires a gradual accumulation of mutations in a number of different genes—different for different cancers, but usually at least five—helps to explain the well-known phenomenon of tumor progression, whereby an initial mild disorder of cell behavior evolves gradually into a full-blown cancer.

- Chronic myelogenous leukemia provides a clear example.

- It begins as a disorder characterized by a nonlethal overproduction of white blood cells and continues in this form for several years before changing into a much more rapidly progressing illness that usually ends in death within a few months.

- Carcinomas and other solid tumors are thought to evolve in a similar way.

- Although many such cancers in humans are not diagnosed until a relatively late stage, in some cases it is possible to observe the earlier steps. Cancers of the uterine cervix (the neck of the womb) are one such example, because of the routine screening for this cancer by cervical scraping.



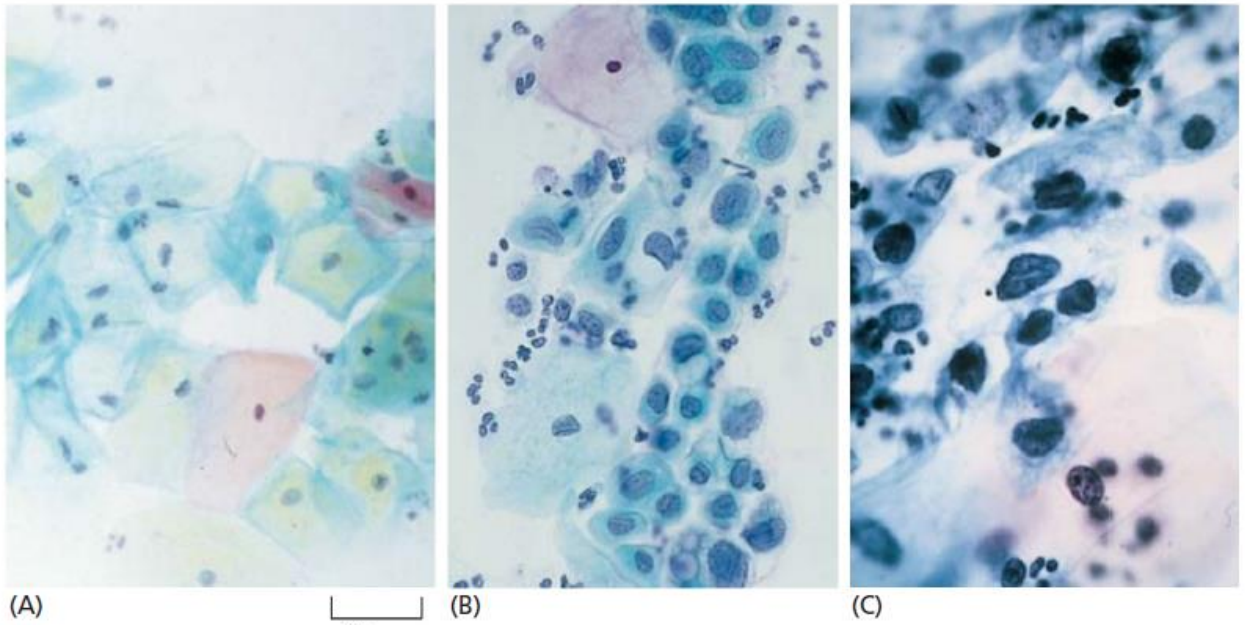


Figure 20–10 Photographs of cells collected by scraping the surface of the uterine cervix (the Papanicolaou or "Pap smear" technique). (A) Normal: the cells are large and well differentiated, with highly condensed nuclei. (B) Precancerous lesion: differentiation and proliferation are abnormal but the lesion is not yet invasive; the cells are in various stages of differentiation, some quite immature. (C) Invasive carcinoma: the cells all appear undifferentiated, with scanty cytoplasm and a relatively large nucleus. For all three panels, debris in the background includes some white blood cells. (Courtesy of Winifred Gray.)

- Without treatment, the abnormal patch of tissue may simply persist and progress no further or may even regress spontaneously.

- In at least 30–40% of cases, however, progression will occur, giving rise, over a period of several years, to a frank invasive carcinoma: the cancer cells cross or destroy the basal lamina, invade the underlying tissue, and may metastasize to local lymph nodes via lymphatic vessels.

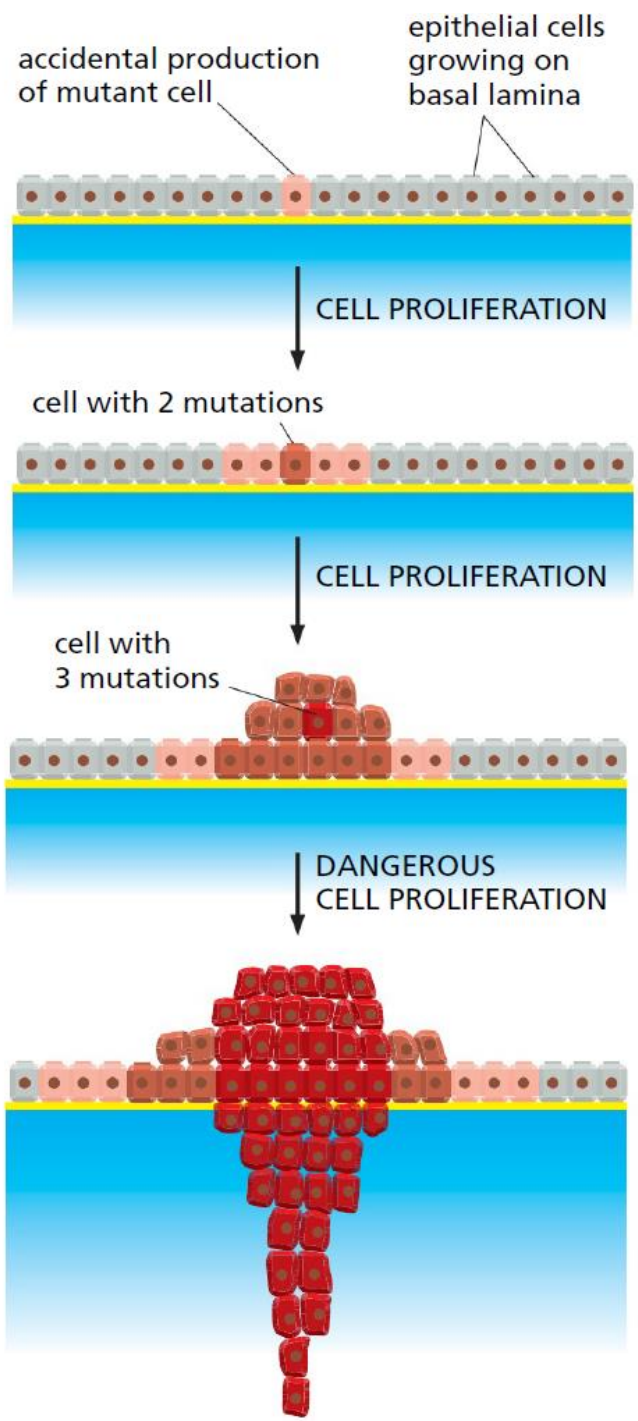
- Surgical cure becomes progressively more difficult as the invasive growth spreads.

- From all the evidence, it seems that cancers arise by a process in which an initial population of slightly abnormal cells, descendants of a single abnormal ancestor, evolve from bad to worse through successive cycles of random inherited change followed by natural selection.

- At each stage, one cell acquires an additional mutation or epigenetic change that gives it a selective advantage over its neighbors, making it better able to thrive in its environment—an environment that, inside a tumor, may be harsh, with low levels of oxygen, scarce nutrients, and the natural barriers to growth presented by the surrounding normal tissues.

- The offspring of the best-adapted cell continue to divide, eventually taking over the tumor and becoming the dominant clone in the developing lesion.

- Tumors grow in fits and starts, as additional advantageous inherited changes arise and the cells bearing them flourish.



- Why are so many changes needed?
- Clearly, large animals have had to evolve a very complex set of regulatory mechanisms to keep their cells in check.
- Without multiple controls, inevitable errors in the maintenance of DNA sequences would produce numerous tumors early in life and quickly destroy any large multicellular organism.
- Thus, we should not be surprised that cells employ multiple regulatory mechanisms to help them maintain tight and precise control over their behavior, and that many different regulatory systems have to be disrupted before a cell can throw off its normal restraints and behave as an asocial cancer cell.

- In general, the rate of evolution in any population of organisms on Earth would be expected to depend mainly on four parameters:

- (1) the mutation rate, that is, the probability per gene per unit time that any given member of the population will undergo genetic change;

- (2) the number of reproducing individuals in the population;

- (3) the rate of reproduction, that is, the average number of generations of progeny produced per unit time; and

- (4) the selective advantage enjoyed by successful mutant individuals, that is, the ratio of the number of surviving fertile progeny they produce per unit time to the number of surviving fertile progeny produced by nonmutant individuals.

- The same types of factors are also crucial for the evolution of cancer cells in a multicellular organism, except that both genetic and epigenetic changes help drive the evolutionary process.

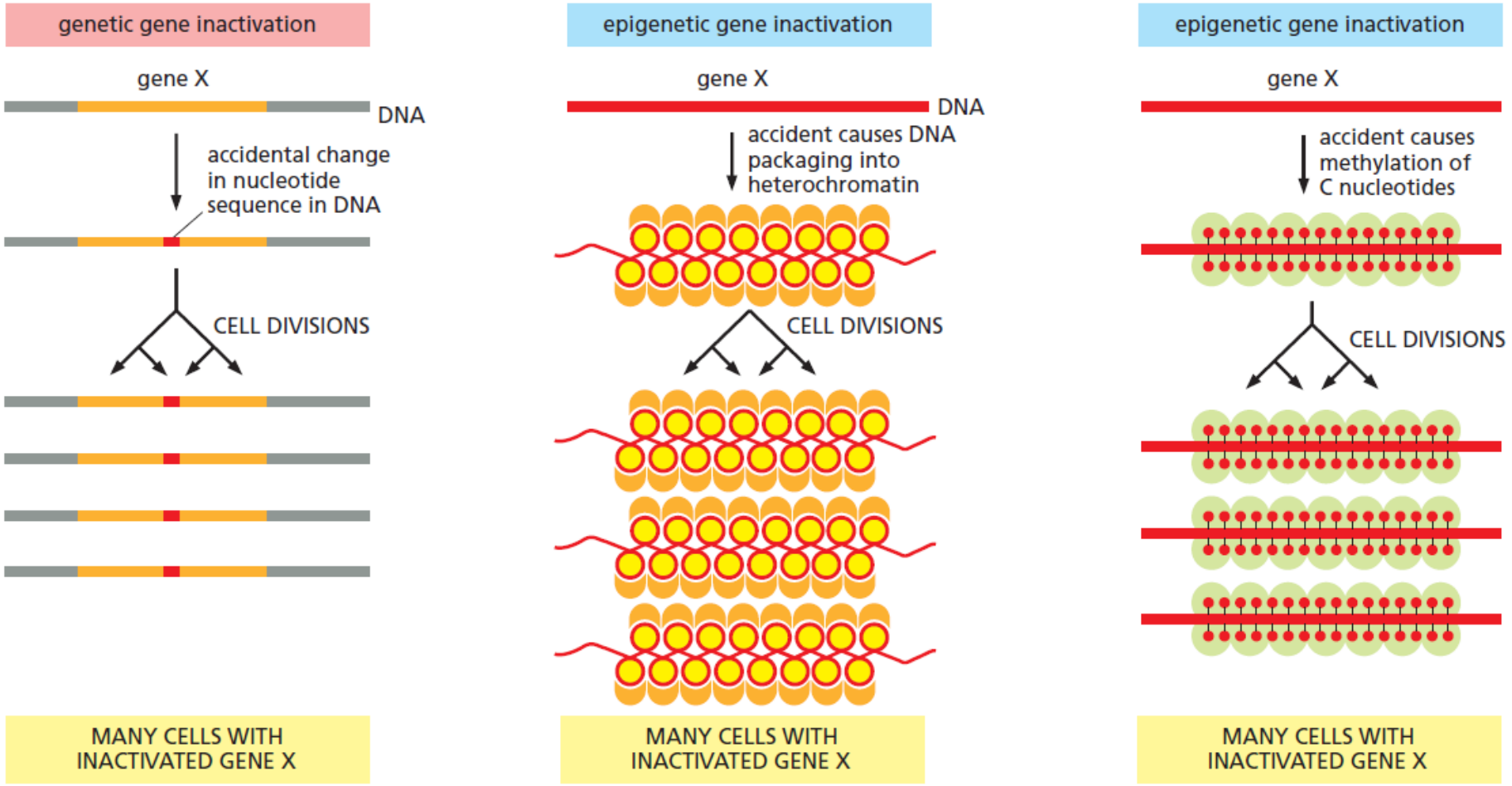
- For many years, pathologists have used an abnormal appearance of the cell nucleus to identify and classify cancer cells in tumor biopsies.

- For example, cancer cells sometimes contain an unusually large amount of heterochromatin—a condensed form of interphase chromatin that silences genes.

- We now understand some of the molecular mechanisms involved in forming this chromatin, and it is possible to associate new heterochromatin formation with the epigenetic silencing of specific genes that would otherwise block tumor progression.

- Many of the mutations that make a cell cancerous alter the proteins that determine chromatin structures.

- Analyses reveal that a large amount of DNA methylation also occurs on selected genes during tumor progression.


genetic gene inactivation
gene X
DNA
accidental change in nucleotide sequence in DNA
CELL DIVISIONS
MANY CELLS WITH INACTIVATED GENE X
epigenetic gene inactivation
gene X
DNA
accident causes DNA packaging into heterochromatin
CELL DIVISIONS
MANY CELLS WITH INACTIVATED GENE X
epigenetic gene inactivation
gene X
accident causes methylation of C nucleotides
CELL DIVISIONS
MANY CELLS WITH INACTIVATED GENE X

- Most human cancer cells accumulate genetic changes at an abnormally rapid rate and are said to be genetically unstable.
- This instability can take various forms.
- Some cancer cells are unable to repair certain types of DNA damage or to correct replication errors of various kinds.
- These cells tend to accumulate more point mutations or other DNA sequence changes than do normal cells.
- Other cancer cells fail to maintain either the number or the integrity of their chromosomes, and they consequently accumulate gross abnormalities in their karyotype that are visible at mitosis.
- The genetic instability is further amplified when some of the DNA changes alter epigenetic control mechanisms in ways that produce extra heterochromatin and DNA methylation.

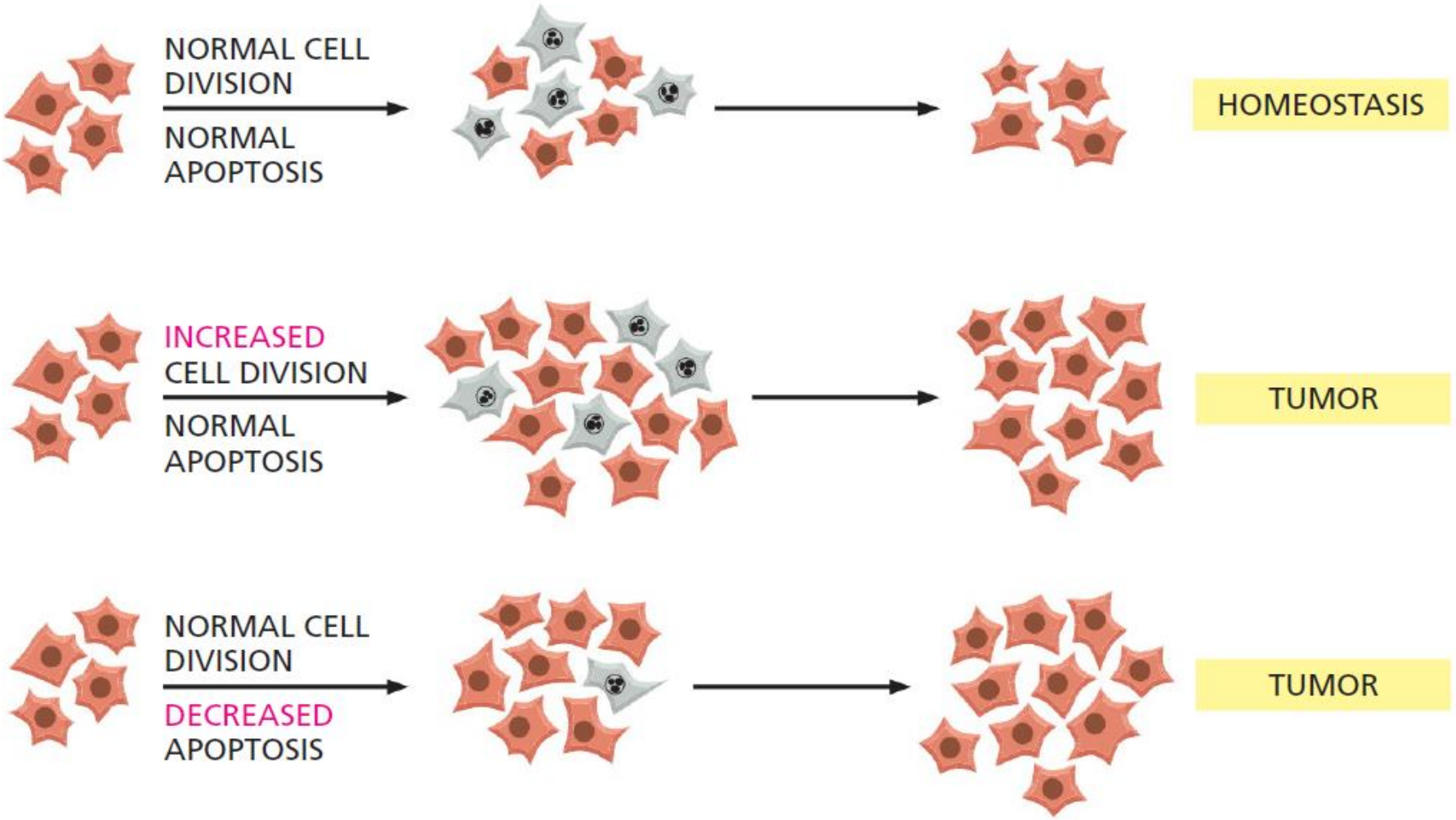
- Cancerous growth often depends on defective control of cell death, cell differentiation, or both.

- Just as an increased mutation rate per cell can raise the probability of cancer, so can any circumstance that increases the number of proliferating cells available for mutating.

- People who are clinically obese, for example, have a strongly increased risk of many types of cancer, compared with people of normal weight; and this is presumably due, in part at least, to an increase in both the number of cells in the body and the rate at which these cells divide when overnourished or overstimulated by growth factors.

- The same principle applies to both cancer initiation and cancer progression: the bigger the clone of altered cells resulting from an early inherited change, the greater the chance that at least one of these cells will undergo an additional mutation or epigenetic change that will allow the cancer to progress.

- Thus, at every stage in the development of cancer, any condition that helps the altered cells to increase in number favors the progression of the tumor.


NORMAL CELL DIVISION
NORMAL APOPTOSIS
HOMEOSTASIS
INCREASED CELL DIVISION
NORMAL APOPTOSIS
TUMOR
NORMAL CELL DIVISION
DECREASED APOPTOSIS
TUMOR

- Many normal human cells have a built-in limit to the number of times they can divide when stimulated to proliferate in culture: they permanently stop dividing after a certain number of population doublings (25–50 for human fibroblasts, for example).

- This cell-division-counting mechanism generally depends on the progressive shortening of the telomeres at the ends of chromosomes, which eventually changes their structure.

- The replication of telomere DNA during S phase depends on the enzyme telomerase, which maintains the special telomeric DNA sequence and promotes the formation of protein cap structures that protect the chromosome ends.

- Because many proliferating human cells (but not stem cells) are deficient in telomerase, their telomeres shorten with every division, and their protective caps deteriorate.

- Eventually, the altered chromosome ends trigger a permanent cell-cycle arrest.

- Human cancer cells avoid this in two ways.

- First, they acquire genetic and epigenetic changes that disable the checkpoint control so that the cells continue to cycle even when telomeres become uncapped.

- Mutations that inactivate the p53 pathway have this effect and are very common in cancer cells.

- As another strategy to escape, cancer cells often maintain telomerase activity as they proliferate, so that their telomeres do not shorten or become uncapped.

- Metastasis is the most deadly—and least understood—aspect of cancer, being responsible for 90% of cancer-associated deaths.

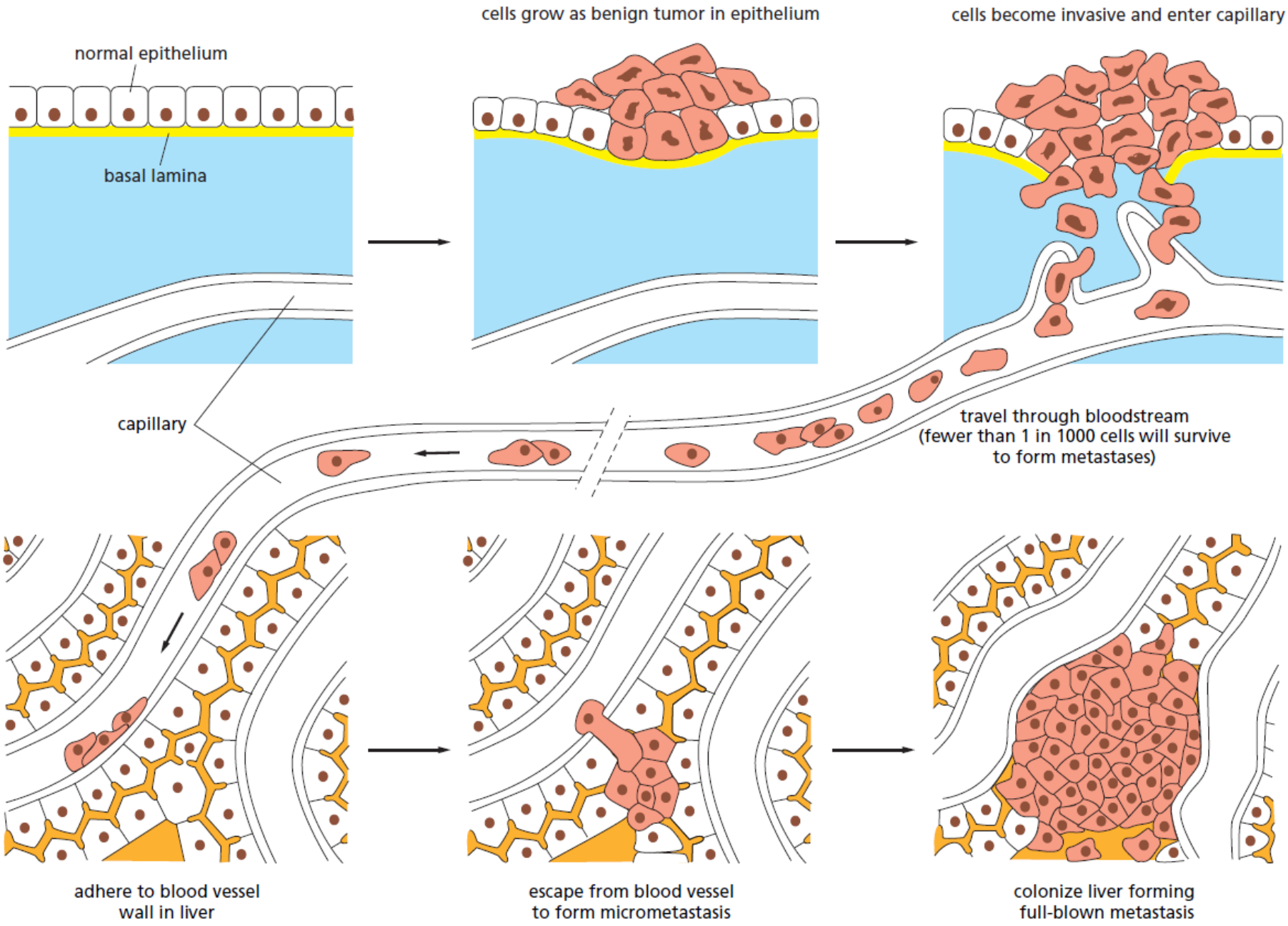
- By spreading throughout the body, a cancer becomes almost impossible to eradicate by either surgery or localized irradiation.

- Metastasis is itself a multistep process: the cancer cells have to invade local tissues and vessels, move through the circulation, leave the vessels, and then establish new cellular colonies at distant sites.

- Each of these events is, in itself, complex, and most of the molecular mechanisms involved are not yet clear.

- For a cancer cell to metastasize, it must break free of constraints that keep normal cells in their proper places and prevent them from invading neighboring tissues.

- Invasiveness is thus one of the defining properties of malignant tumors, which show a disorganized pattern of growth and ragged borders, with extensions into the surrounding tissue


normal epithelium
basal lamina
cells grow as benign tumor in epithelium
cells become invasive and enter capillary
capillary
travel through bloodstream
(fewer than 1 in 1000 cells will survive
to form metastases)
adhere to blood vessel
wall in liver
escape from blood vessel
to form micrometastasis
colonize liver forming
full-blown metastasis

- The next step in metastasis—the establishment of colonies in distant organs—is a complex, slow, and inefficient operation; few cells achieve it.

- Before it can metastasize successfully, a cell must penetrate a blood vessel or a lymphatic vessel by crossing the basal lamina and the endothelial lining of the vessel so as to enter the blood or lymph, exit from a vessel elsewhere in the body, and grow in the new site, forming at first a small clump of cells known as a micrometastasis.

- To complete the metastatic process, some of these micrometastases must produce cells that survive and proliferate extensively in the new environment, a difficult process known as colonization.

- In addition to all the requirements just described, to grow large, a tumor must recruit an adequate blood supply to ensure that it gets sufficient oxygen and nutrients.

- Thus, angiogenesis, the formation of new blood vessels, is required for tumor growth beyond a certain size.

- Like normal tissues, tumors attract a blood supply by secreting angiogenic signals.

- These signals are produced in response to hypoxia, which begins to affect the cells as the tumor enlarges beyond a millimeter or two in diameter.

- The hypoxia activates an angiogenic switch to increase the blood supply by provoking an increase in the level of Hypoxia Inducible Factor-1a (HIF-1a); this protein, in turn, activates the transcription of genes that encode pro-angiogenic factors, such as vascular endothelial growth factor (VEGF).

- These are secreted proteins that attract endothelial cells and stimulate the growth of new blood vessels.

- The vessels not only help supply the tumor with nutrients and oxygen, but also provide an escape route for its cells to metastasize.

- Clearly, to produce a cancer, a cell must acquire a range of aberrant properties—a collection of subversive new skills—as it evolves. We can draw up a short list of the key behaviors of cancer cells in general:

- 1. They are more self-sufficient than normal cells for their growth and proliferation.
- 2. They are relatively insensitive to anti-proliferative extracellular signals.
- 3. They are less prone than normal cells to undergo apoptosis.
- 4. They are defective in the intracellular control mechanisms that normally stop cell division permanently in response to stress (such as hypoxia) or DNA damage.
- 5. They induce help from the normal stromal cells in their local environment.
- 6. They induce angiogenesis.
- 7. They escape from their home tissues (that is, they are invasive) and survive and proliferate in foreign sites (that is, they metastasize).
- 8. They are genetically unstable.
- 9. They either produce telomerase, or acquire another way of stabilizing their telomeres.