Neoplasia is a very important topic in pathology because neoplasms are both common and serious diseases. A neoplasm literally means a new growth, and this term is used interchangeably with a tumor (swelling) because most tumors present as a mass. Oncology (Greek oncos = tumor) is the study of neoplasms. A neoplasm is defined as "an abnormal tissue proliferation, which exceeds that of adjacent normal tissue. This proliferation continues even after removing the causative agent". The persistence of proliferation is the result of heritable genetic changes in the constituent cells; these provide the neoplastic cells with a growth advantage. In other words the neoplasm becomes autonomous i.e. independent of physiologic growth stimuli and inhibitors. The entire population of cells within any tumor originates from a single cell referred to as stem cell or tumor initiating cell (T-IC). This cell has sustained the initial genetic changes (mutations). A given tumor, therefore, consists of T-IC (the ancestor) and its progeny forming a clone of cells and hence tumors are said to be clonal.

**NOMENCLATURE OF NEOPLASMS**

In addition to the neoplastic cells, all tumors have a second component called the stroma that is made up principally of connective tissue and blood vessels. The stroma is vital to the neoplastic cells; it provides them not only with adequate blood supply but also mechanical support (scaffolding). Additionally, there seems to be a cross talk between the stroma and the neoplastic cells that directly influence the growth of the neoplasm for e.g. neoplastic cells release substances that stimulate endothelial cells to form new vessels within the tumor (neovascularization) & endothelial cells release growth factors that encourage tumor cell growth. The relative proportions of the two components vary in different tumors. This variable contribution of the two determines the consistency of any given tumor. In some tumors, the stroma is scant i.e. the tumors consist predominantly of neoplastic cells; these neoplasms are soft and fleshy in consistency. Conversely, the neoplastic cells may stimulate the formation of abundant fibrotic stroma, referred to as desmoplasia. This desmoplasia imparts a hard (scirrhous) or even stony hard consistency to the tumor. An example of the latter is carcinoma of the breast, which has been likened to unripe pear. However, it should be realized that despite the fact that both components (neoplastic cells & stroma) are complementary in their significance to the wellbeing of the tumor, the nomenclature of tumors is based on their neoplastic cells.

**Benign Tumors**

In general, benign tumors are named by attaching the suffix -oma to the cell of origin. Benign mesenchymal tumors generally follow this rule. For example, a benign tumor of fibroblasts is called fibroma, a cartilaginous tumor is
chondroma, (Fig. 8-1) and a tumor of osteoblasts is osteoma. The nomenclature of benign epithelial tumors is more complex in that they are variously classified according to their

a. Cells of origin  

b. Microscopic &/or macroscopic (naked eye) appearance

Adenoma is the term applied to a benign epithelial neoplasm that forms microscopically recognizable glandular structures e.g. renal cell adenoma & thyroid follicular adenoma. (Fig. 8-2) However, tumors derived from glandular tissues are also called adenomas even though they do not reproduce glandular structures e.g. some thyroid follicular adenomas are composed of packed trabeculae (bands) or cords of follicular epithelial cells. A papilloma is a benign epithelial neoplasm producing microscopically or macroscopically visible finger-like (warty) projections from epithelial surfaces e.g. squamous cell papilloma of the skin & larynx & transitional cell papilloma of the urinary bladder. (Fig. 8-3) A cystadenoma is an adenoma that form large cystic space (or spaces), e.g. ovarian cyst adenoma. A papillary cystadenoma is similar to cyst adenoma but has in addition papillary (warty) projections that protrude into the cystic spaces, e.g. ovarian papillary cystadenoma. (Fig. 8-4) A polyp is a benign neoplasm that forms a macroscopically visible projection above a mucosal surface (e.g. gastric, colonic, and laryngeal polyps) or skin. (Fig. 8-5) Malignant tumors may present as bulging masses with nodular surface (simulating multiple fused polyps); these are usually referred to as polypoid cancers.

Malignant Tumors

Cancer is a term applied for any malignant tumor. The nomenclature of malignant tumors follows essentially the same rules used for benign neoplasms but with certain additions. Sarcomas are malignant tumors that arises from or differentiating towards mesenchymal cells. Generally, sarcomas have scant connective tissue stroma; they are fleshy in consistency (Greek sar = fleshy). Examples include fibrosarcoma (fibroblasts), liposarcoma (lipocytes), leiomyosarcoma (smooth muscle cells), and rhabdomyosarcoma (striated muscle cells).

Carcinoma is a malignant neoplasm that either arises from or differentiates towards epithelial cells derived from any one of the three germ layers. Thus, a cancer arising in or differentiating towards epidermal epithelial cells (ectoderm) is a carcinoma and a cancer derived from or differentiates towards renal tubules (mesoderm) is also carcinoma. Similarly malignant tumors originating from or differentiating towards the endodermally derived epithelial cells that line the gastrointestinal or respiratory tracts are similarly called carcinomas. Carcinomas may be further qualified according to their pattern of arrangements. A carcinoma with a microscopic glandular growth pattern is termed adenocarcinoma, and one producing recognizable squamous cells arising in any epithelium of the body (e.g. skin, esophagus or cervix uteri) is termed a squamous cell carcinoma. Additionally, it is a common practice to specify, when possible, the organ of origin (e.g., a renal cell adenocarcinoma or bronchial squamous cell carcinoma). Undifferentiated (anaplastic) malignant
**tumor** refers to a cancer composed of undifferentiated (anaplastic) cells, which have no enough microscopic criteria to indicate their site of origin or differentiation. Sometimes a single line of neoplastic cells show divergent differentiations, creating what is called **mixed tumors** e.g. mixed salivary gland tumors. These tumors have benign epithelial/myoepithelial cells as their basic component. These cells show, among others, glands & tubules that scatter within a myxoid stroma, hence by definition the tumor is adenoma. However, they may also show, in addition, squamous nests and sometimes islands of cartilage and even bone. All these elements are believed to arise from the native epithelial/myoepithelial cells, that is why these neoplasms because of their diverse morphology, are also termed **pleomorphic adenomas**. (Fig. 8-6)

**Lymphomas and leukemias** are malignancies derived from hematopoetic cells. **Germ cell tumors** are derived from totipotent cells; these cells have the inherent capacity of divergent differentiations. In adults, tumors derived from these cells are most often found in the testicle and ovary, however, they may also be seen as primary tumors within the midline structures e.g. mediastinum, retroperitoneum and sacrococcygeal regions. A **teratoma** is a germ cell tumor, which in contrast to the previously mentioned neoplasms, is made up of a variety neoplastic cell types that represent more than one germ layer, usually all the three. The neoplastic totipotent cells of teratomas differentiate along various germ lines, producing tissues that can be identified, for e.g. as skin (ectodermal), muscle, fat, (mesodermal) and gut epithelium (endodermal). Some times a tooth, brain tissues, bronchial structures or any other tissue may be present. Teratomas are commonly seen in the ovary and since these ovarian tumors are commonly cystic they are designated as **cystic teratomas**, and because the skin (and its adnexae such as hair & sebaceous glands) is a major component of such tumors they are also have the alternative name of **dermoid cysts**. (Fig. 8-7)

Having described above the various designations of tumors, what remains in the context of nomenclature of neoplasia is the presence of some inappropriate designations that do not follow the above principles. Never the less, their usage continues by tradition. For generations, carcinomas of melanocytes have been called **melanomas**, although correctly they should be referred to as melanocarcinomas. Similarly, a special type of testicular germ cell carcinoma is called **seminoma**. Another example is **hepatoma** (correctly a hepatocellular carcinoma). It should also be kept in mind two additional terms, namely choristoma & hamartoma, both although ending with the suffix –oma, are not true neoplasms but rather a reflection of anomalous growth development. **Choristoma (ectopia; heterotopia)** (Gr. choristos: separated) refers to the presence of microscopically normal tissues in an unexpected location, for example, a rest (a remnant) of adrenal gland under the kidney capsule, or pancreatic tissue in the wall of the esophagus, stomach or small intestine. (Fig. 8-8) They are called **choristomas** because they may form masses or nodules that mimic neoplasms grossly. A **Hamartoma** refers to aberrant (abnormal) differentiation that produces a mass of disorganized but mature specialized tissues pertinent to the particular site in which they occur. Thus, a lung
hamartoma may contain islands of cartilage, blood vessels, bronchial-type structures, and lymphoid tissue, all normally present in the lung but they are displayed in a disorganized fashion. Sometimes one element predominates so that the lesion appears purely cartilaginous or purely angiomatous (made up of blood vessels; angioma).

The nomenclature of tumors is important because tumors with specific names have definite clinical inferences, even among tumors arising from the same tissue. Seminoma is a form of testicular germ cell carcinoma that tends to remain localized within that organ for sometime, and then show a local spread to para-aortic lymph nodes. Additionally, these tumors are extremely radiosensitive and can be eradicated by radiotherapy. By contrast, embryonal carcinoma, another germ cell testicular tumor, differs from seminoma by being more aggressive; it is neither radiosensitive nor tends to remain localized. It invades locally beyond the confines of the testis and spreads rapidly throughout the body. There are also other varieties of testicular neoplasms that differ in their behavior from the above two, and so using the term "cancer" to cover all malignant testicular neoplasms tells little of their diverse natural histories (expected clinical behavior).

<table>
<thead>
<tr>
<th>Tissue of Origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMPOSED OF ONE PARENCHYMAL CELL TYPE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumors of Mesenchymal Origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective tissue and derivatives</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td></td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td></td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td></td>
<td>Osteoma</td>
<td>Osteogenic sarcoma</td>
</tr>
<tr>
<td><strong>Endothelial and Related Tissues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Lymph vessels</td>
<td>Lymphangioma</td>
<td>Lymphangiosarcoma</td>
</tr>
<tr>
<td>Synovium</td>
<td>Synovial sarcoma</td>
<td></td>
</tr>
<tr>
<td>Mesothelium</td>
<td>Mesothelioma</td>
<td></td>
</tr>
<tr>
<td>Brain coverings</td>
<td>Meningioma</td>
<td>Invasive meningioma</td>
</tr>
<tr>
<td><strong>Blood Cells and Related Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematopoietic cells</td>
<td>Leukemias</td>
<td></td>
</tr>
<tr>
<td>Tissue of Origin</td>
<td>Benign</td>
<td>Malignant</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Striated</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Tumors of Epithelial Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified squamous</td>
<td>Squamous cell papilloma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Basal cells of skin or adnexa</td>
<td></td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Epithelial lining of glands or ducts</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Papilloma</td>
<td>Papillary carcinomas</td>
</tr>
<tr>
<td></td>
<td>Cystadenoma</td>
<td>Cystadenocarcinoma</td>
</tr>
<tr>
<td>Respiratory passages</td>
<td>Bronchial adenoma</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Renal epithelium</td>
<td>Renal tubular adenoma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Liver cells</td>
<td>Liver cell adenoma</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Urinary tract epithelium</td>
<td>Transitional-cell papilloma</td>
<td>Transitional-cell carcinoma</td>
</tr>
<tr>
<td>(transitional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental epithelium</td>
<td>Hydatidiform mole</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Testicular epithelium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(germ cells)</td>
<td></td>
<td>Seminoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Tumors of Melanocytes</td>
<td>Nevus</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>MORE THAN ONE NEOPLASTIC CELL TYPE—MIXED TUMORS, USUALLY DERIVED FROM ONE GERM CELL LAYER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Pleomorphic adenoma (mixed tumor of salivary origin)</td>
<td>Malignant mixed tumor of salivary gland origin</td>
</tr>
<tr>
<td>Renal anlage</td>
<td></td>
<td>Wilms tumor</td>
</tr>
<tr>
<td>MORE THAN ONE NEOPLASTIC CELL TYPE DERIVED FROM MORE THAN ONE GERM CELL LAYER—TERATOGENOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totipotential cells in gonads or in embryonic rests</td>
<td>Mature teratoma, dermoid cyst</td>
<td>Immature teratoma, teratocarcinoma</td>
</tr>
</tbody>
</table>
BIOLOGY OF TUMOR GROWTH
Malignant tumors differ from benign ones by four features that in fact reflect their natural history (expected behavior); these are
I. Malignant transformation of the target cells
II. Growth rate of the transformed cells
III. Local invasion
IV. Distant metastases

I. MALIGNANT TRANSFORMATION

Malignant transformation of target cells is associated with certain microscopic features that are usually used to differentiate benign from malignant neoplasms. These features are collectively come under the heading of differentiation and anaplasia.

**Differentiation** signifies "*the extent to which neoplastic cells resemble comparable normal cells*". The degree of tumor differentiation is represented by a spectrum according to which neoplasms are divided in to
- Very well differentiated
- Well differentiated
- Moderately differentiated
- Poorly differentiated
- Undifferentiated (Anaplastic)

**Very well differentiated neoplasm** is the one in which the neoplastic cells are almost identical morphologically to the native normal cells. This is generally encountered with benign neoplasms. For example, the neoplastic cells in a leiomyoma of the uterus resemble very closely the normal native myometrial cells. This resemblance is to such a degree that it may be impossible to differentiate microscopically neoplastic cells from native normal myometrial cells. It is only the gathering of these cells into a tumor mass that discloses the neoplastic nature of the lesion. *(Fig. 8-9)* What is just said about leiomyoma is also applicable to lipoma e.g. of the skin where the neoplastic lipocytes cannot be differentiated from those of the normal subcutaneous adipose tissue. *(Fig. 8-10)*

Malignant neoplasms are generally divided into four categories depending on their degree of differentiation, these are

1. **Well-differentiated neoplasms** i.e. composed of cells resembling closely comparable normal cells of the tissue of origin. Certain well-differentiated thyroid follicular carcinomas (adenocarcinomas), for example, may form almost normal-appearing follicles, and the cells of some squamous cell carcinomas contain cells that do not differ significantly from normal squamous
epithelial cells. (Fig. 8-11) Thus, the microscopic diagnosis of malignancy in well-differentiated neoplasms can be quite difficult.

2. **Poorly differentiated neoplasms**, in contrast, are composed of cells that barely resemble the normal cells of origin. However, some resemblance occurs focally i.e. in some parts of the tumor, thus allowing the tumor to be assigned to a particular cell of origin or differentiation.

3. **Moderately differentiated neoplasms** occupy a morphological position that lie between well-differentiated & poorly-differentiated tumors.

4. **Undifferentiated (anaplastic) neoplasms**: anaplasia signifies total lack of differentiation, and thus anaplastic cells have primitive appearance (unspecialized morphology) that can not be assigned to any of the normal mature cells. (Fig. 8-12)

**Morphologic features of undifferentiated (anaplastic) malignant cells include**

1. **Pleomorphism**, i.e. variations in the size and shape of the neoplastic cells and their nuclei. In anaplastic cancers, some cells are many times larger than their neighboring extremely small cells.

2. **Abnormal nuclear morphology**: characteristically the nuclei display
   a. **Hyperchromatism**, which refers to a deep bluish staining of nuclei; this feature is due to their abnormally high content of DNA. In the routine hematoxyline & eosin stain, the abundant DNA extracts more hematoxyline, and so the malignant nuclei appear deep blue in color.
   b. **High nuclear-cytoplasmic ratio** (high N/C); in malignant neoplasms, the nuclei are disproportionately large for the cell size, and thus the nucleus-to-cytoplasm ratio may approach 1:1 instead of the normal 1:4 or 1:6.
   c. **Variations in nuclear shape and abnormal chromatin clumping and distribution**: the nuclear shape is very variable, and the chromatin is coarsely clumped and distributed along the nuclear membrane. Normal nuclei are vesicular i.e. have fine, evenly distributed chromatin granules.
   d. **Large prominent nucleoli** are sometimes seen within malignant nuclei.

3. **Frequent mitoses including abnormal ones**: undifferentiated malignant cells usually possess large number of mitoses, reflecting their high proliferative activity. The presence of mitoses, however, does not necessarily indicate that a tumor is malignant or that the tissue is neoplastic. Many normal tissues exhibit rapid cell turnover & hence their constituent cells show frequent mitoses e.g. the normal bone marrow cells. The adaptive hyperplastic tissue response also shows frequent mitotic figures. More important as a morphologic feature of malignancy is the presence of atypical mitotic figures, e.g. tripolar, quadripolar, or multipolar mitoses (instead of the normal bipolar spindles)

4. **Loss of polarity**: this means disturbed orientation of the cells. In malignancy, sheets of tumor cells grow in disorganized fashion. Normal epidermis shows normally oriented stratified constituent cells; from below up there are the basal cells followed by spinous cells then granular cells and finally the upper most layer of flattened, keratinized cells. Although differentiated squamous cells carcinoma tend to recapitulate to some extent this arrangement, it is totally
lacking in poorly differentiated and undifferentiated examples i.e. there is no longer the normal architectural stratification that is seen in the normal skin.

5. Other changes

a. Formation of tumor giant cells: (Fig. 8-13) some of these abnormally large cells possess only a single huge pleomorphic nucleus; others have two or more nuclei. These malignant giant cells are not to be confused with the inflammatory Langhan or foreign body giant cells; these are derived from macrophages and contain many small, normal-appearing nuclei. In cancer giant cells, the nuclei show malignant features, for e.g. they are hyperchromatic and large in relation to the cell size.

b. Foci of ischemic necrosis: dividing and growing tumor cells require adequate blood supply for their survival. In many anaplastic tumors, because of the rapid proliferation of the constituent cells and/or scant stromal vascularity, the tumor may overrun the available blood supply. This leads to large areas of ischemic necrosis. The presence of necrotic areas within a malignant tumor is a poor prognostic sign, since it usually reflects an aggressive rapidly growing malignancy.

Dysplasia

Having mentioned the features of malignancy, it is pertinent to comment on a closely related condition designated dysplasia. Dysplasia literally means disordered growth. This change is encountered principally in epithelial membranes (e.g. the squamous epithelium of the cervix, skin, and metaplastic bronchial mucosa) and it is characterized by changes that include

1. Pleomorphism and loss of orientation of the affected cells
2. Frequent presence of hyperchromatic and large nuclei
3. Unusually abundant mitotic figures; although these are almost invariably of normal patterns (bipolar), frequently, however, the mitoses appear in abnormal locations within the epithelium, for e.g. in dysplastic stratified squamous epithelium; mitoses are not limited to the basal layers as is the case normally, but appear at all levels including the surface cells.

According to the severity & extent of the above changes, dysplasias are graded into mild, moderate and severe; recently dysplasia is also divided into low-grade and high-grade. When the dysplastic changes are severe and involve the entire thickness of the epithelium, it is considered a pre-invasive neoplasm and is referred to as carcinoma in situ. (Fig. 8-14) Once the tumor cells move beyond the normal confines through breaching the limiting basement membrane, the tumor is considered invasive carcinoma. Dysplastic changes are often found adjacent to foci of invasive carcinoma, and in some situations, such as in long-term cigarette smokers, severe epithelial dysplasia of the bronchial epithelium frequently precedes the appearance of cancer. However, dysplasia does not necessarily progress to cancer. Mild to moderate dysplastic changes that do not involve the entire thickness of epithelium may be reversible, and with the removal of the inciting cause, the epithelium may revert to normal. Severe dysplasia is much more serious because of its more intimate association with invasive carcinomas.
II. GROWTH RATE OF THE TRANSFORMED CELLS

The growth rate of neoplasms (i.e. how rapidly they increase in size) influences not only their clinical outcome but also their response to therapy. Any neoplasm is now considered clonal i.e. originating from one (or at most few) initially transformed cells (I-TC). For the tumor to be clinically detectable (at least 1 g in wt), the I-TC and its progeny (collectively referred to as tumor cell population) must undergo at least 30 population doublings. Further 10 population doublings; however, are required to produce a mass with a maximal size compatible with survival (a weight of 1 Kg). These calculations mean that by the time a solid tumor is clinically detected (at least 1 g in wt); it has already completed a major portion (75%) of its life cycle. (Fig. 8-15) The larger the cancer, the more difficult it becomes to treat and control. Accordingly, diagnostic investigations are needed to detect early cancers & this is the prime goal of screening programs e.g. that of the cervix (Pap smear) & breast (mammography).

The growth rate of a tumor is determined by three main factors
1. The doubling time of tumor cells (length of the cell cycle)
2. The size of the replicative pool. (Replicative pool refers to that part of the tumor made up of exclusively of dividing cells).
3. The rate at which cells leave the growing tumor

The cell-cycle controls are disturbed in most neoplasms and this leads to an increase in the number of cells that enter into the replicative pool. The size of the replicative pool relative to the total size of the tumor is referred to as the growth fraction because this fraction is the prime determinant of tumor expansion. Thus, a tumor with a large growth fraction grows more rapidly than that with a small one. Commonly, the growth of tumors is not due to a shortening of cell-cycle time but because more cells enter into the replicative pool of the cell cycle. Studies suggest that during the early phase of tumor growth, the vast majority of transformed cells are in the replicative pool. As tumors continue to grow, cells leave this pool in ever-increasing numbers due to
1. Shedding
2. Necrosis due to lack of nutrients
3. Apoptosis
4. Differentiation
5. Reversion to G0 (Fig. 8-16)

Ultimately the rate at which a neoplasm grows is determined by an excess of cell production over cell loss. Some leukemias, lymphomas and small cell undifferentiated carcinomas, have a high growth fraction, and their clinical course are, therefore, rapid. By comparison, many common tumors such as cancers of the colon and breast have low growth fractions, and cell production exceeds cell loss only marginally; that is why they tend to grow relatively slowly. Several important practical lessons can be deduced from studying tumor cell kinetics:
1. The growth fraction has a profound effect on the susceptibility of the cancer to chemotherapy. This is because most anticancer agents kill cells that are in the replicative pool (dividing cells). That is why certain aggressive lymphomas) that contain large pools of dividing cells melt away and even cured with chemotherapy. On the other hand, a tumor that contains 5% of all of its constituent cells in the replicative pool (e.g. carcinomas of the colon and breast) will not only be slow growing but also relatively resistant to treatment with chemotherapeutic agents. One strategy employed to overcome this problem is first to shift tumor cells from G0 into the replicative pool. This can be accomplished by either surgical removal of the accessible major portion of the cancer (debulking) &/or by radiation. Such considerations form the basis of combined treatment protocols (triple therapy: radiation, surgery, and chemotherapy).

2. In general, the growth rate of tumors correlates inversely with their level of differentiation, that is why most malignant tumors grow more rapidly than do benign ones; the latter are highly differentiated tumors. Similarly, poorly differentiated malignancies grow more rapidly than their well-differentiated counterpart.

3. There are factors that affect the growth rate of various neoplasms whether benign or malignant; these include hormonal stimulation, adequacy of blood supply, etc. For example, during pregnancy, uterine leiomyomas frequently increase in size. Conversely, after menopause, these neoplasms may atrophy and become replaced largely by collagenous, sometimes calcified fibrous tissue. Such changes reflect the responsiveness of the tumor cells to the circulating levels of steroid hormones, particularly estrogens. This hormonal responsiveness is due to the possession of the neoplastic cells of certain receptors that can be hormonally-stimulated. Similarly, a significant number of breast and uterine adenocinomas are estrogen sensitive.

4. Some cancers show a wide variation in their growth rates. Some malignant tumors grow slowly for years and then suddenly increase in size and explosively disseminate to cause death within a few months. This is probably the result of the occurrence of an aggressive subclone of transformed cells. This phenomenon is referred to as dedifferentiation.

Cancer Stem Cells
A neoplasm contains a heterogeneous population of cells that originate from the clonal growth of a single cell termed stem cell. Stem cells are thought to be the initial targets of neoplastic transformation. They are capable of initiating & sustaining cancer growth. Cancer stem cells (tumor-initiating cells, T-IC) have been identified in breast tumors and acute myeloid leukemia. They have been found to constitute 1- 2% of the total cell population in these tumors. Cancer stem cells, similar to their normal counterparts, have a low rate of replication. Thus, cancer therapeutic agents that may efficiently kill the replicating progeny of cancer cells, leave the T-IC in place. This is the likely explanation of tumor recurrence after treatment.
III. LOCAL INVASION
Benign tumors differ from malignant ones by their slow rate of growth and as cohesive masses, thus, benign tumors usually (not always) develop a rim of compressed connective tissue called fibrous capsule, which separates them from the native host tissue. An example is fibroadenoma of the breast. (Fig. 8-17) This tumor on clinical examination is well-defined and typically mobile mass. Benign tumors remain confined to the site of origin without having the ability to invade locally or metastasize to distant sites. In contrast, most malignant tumors are invasive and can be expected to penetrate and destroy the underlying tissues i.e. they are not surrounded by a capsule. Fixation of a breast mass on clinical examination makes it suspicious for malignancy (cf. fibroadenoma). It is this invasiveness that makes surgical resection of cancers difficult. (Fig. 8-18) It is necessary during surgery to remove a margin of apparently normal tissues (margin of safety) adjacent to infiltrative cancer. One of the prime functions of the pathologist is to indicate, in his report of a surgically excised malignant tumor, of whether the tumor is totally removed (free excision margins) or not incompletely excised (positive excision margins). In the latter instance recurrence of the tumor is a strong possibility. Some cancers progress from a pre-invasive stage (carcinoma in situ); this commonly occurs in carcinomas of the skin, breast, and uterine cervix. In situ epithelial cancers display the cytologic features of malignancy but are devoid of invasion outside the subjacent or encompassing basement membrane.

IV. METASTASIS
By definition metastases are "tumor implants discontinuous with the primary tumor". Metastasis is the only definitive criterion of malignancy because benign neoplasms do not metastasize. Almost all cancers can metastasize. The major exceptions are
1. Most malignant gliomas of CNS (derived from glial cells)
2. Most Basal cell carcinomas of the skin. Rodent ulcer is a clinical descriptive term used for basal cell carcinoma because of their destructive invasiveness. Yet they, as a rule, do not metastasize. (Fig. 8-19) In general, cancers more likely to metastasize are
1. The more aggressive and more rapidly growing
2. Those of large size
Metastatic spread strongly reduces the possibility of cure. The invasiveness of cancers permits them to penetrate into 1. Body cavities 2. Lymphatic vessels 3. Blood vessels
Pathways of Spread
Dissemination of cancers may occur through one of three pathways:
a. Direct seeding of body cavities or surfaces b. Lymphatic spread c. Hematogenous spread
Seeding of Body Cavities and Surfaces
This may occur whenever a cancer, as a result of progressive invasion, penetrates into a natural "open field." Most often involved is the peritoneal cavity, but any other cavity—pleural, pericardial, subarachnoid, and joint space—may be affected. Peritoneal seeding is particularly characteristic of ovarian carcinomas. Sometimes mucus-secreting adenocarcinomas of the appendix fill the peritoneal cavity with a gelatinous (myxoid) neoplastic mass. This finding is referred to as pseudomyxoma peritonei. (Fig. 8-20) Lung and breast carcinomas as well as many other cancers may involve pleural cavity. (Fig. 8-21) Involvement of serous membranes by metastases is associated with pouring of exudates in to these cavities (malignant peritoneal, pleural or pericardial effusion).

Lymphatic Spread
This is the most common pathway for the initial dissemination of carcinomas, but some sarcomas may also use this route. The pattern of lymph node involvement follows the natural routes of lymphatic drainage. Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to ipsilateral axillary lymph nodes. Cancers of the inner quadrants may drain to the nodes along the internal mammary arteries. Thereafter the infraclavicular and supraclavicular nodes may become involved. (Fig. 8-22) Carcinomas of the lung arising in major respiratory passages metastasize first to the hilar-tracheobronchial and mediastinal nodes. In breast cancer, determining the involvement of axillary lymph nodes is very important for assessing the future course of the disease and for selecting suitable therapeutic strategies. Usually, lymphatic spread of breast cancers is assessed by performing a full removal of axillary lymph nodes. Because this procedure is associated with considerable surgical morbidity, a biopsy of sentinel node is often used. A sentinel lymph node is defined as "the first node in a regional lymphatic basin that receives lymph flow from the primary tumor." This node is therefore a representative of the regional lymph nodes status. Assessment of sentinel node has also been used for detecting lymphatic spread of melanomas, colon cancers, and other tumors. Drainage of tumor cell antigens without cancerous cells may induce reactive changes (reactive lymphoid hyperplasia) within the regional nodes causing their enlargement. Therefore, nodal enlargement near a cancer does not necessarily mean dissemination of the primary tumor. Differentiation between the two is only possible through microscopic examination of sections from the excised nodes.

Hematogenous Spread
Hematogenous spread is typical of sarcomas but is also seen with carcinomas. Veins, because of their thinner wall, are more readily penetrated than arteries. With venous invasion, the blood-borne cells follow the venous flow draining the site of the neoplasm. The liver and lungs are most frequently involved by metastases. (Fig. 8-23) This is because all portal area drainage flows to the liver, and all vena cava blood flows to the lungs. Cancers arising in close proximity to the vertebral column often metastasize through the paravertebral plexus of veins, and this pathway is probably the cause of frequent vertebral
(bone) metastases of carcinomas of the thyroid and prostate. Certain cancers have a remarkable tendency for invasion of veins. Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself to grow in a snakelike fashion up the inferior vena cava, sometimes reaching the right side of the heart. Hepatocellular carcinomas often penetrate portal and hepatic venous radicles to grow within them into the main venous channels. Histologic evidence of penetration of small vessels within a primary neoplasm is obviously an ominous feature.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation/anaplasia</td>
<td>Well differentiated; structure sometimes typical of tissue of origin</td>
<td>Some lack of differentiation with anaplasia; structure often atypical</td>
</tr>
<tr>
<td>Rate of growth</td>
<td>Usually progressive and slow; may come to a standstill or regress;</td>
<td>Erratic and may be slow to rapid; mitotic figures may be numerous and</td>
</tr>
<tr>
<td></td>
<td>mitotic figures rare and normal</td>
<td>abnormal</td>
</tr>
<tr>
<td>Local invasion</td>
<td>Usually cohesive expansile well-demarcated masses that do not invade</td>
<td>Locally invasive, infiltrating surrounding tissue; sometimes may be</td>
</tr>
<tr>
<td></td>
<td>or infiltrate surrounding normal tissues</td>
<td>seemingly cohesive and expansile</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Absent</td>
<td>Frequently present; the larger and more undifferentiated the primary,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the more likely are metastases</td>
</tr>
</tbody>
</table>
PRECANCEROUS CONDITIONS
Certain conditions are known to have an increased risk of association with cancer; these have been designated as precancerous conditions. They are divided into two groups

A. Non-neoplastic conditions; examples include
   1. Chronic ulcerative colitis
   2. Chronic atrophic gastritis
   3. Chronic viral B & C hepatitis
   4. Cutaneous actinic keratosis
   5. Leukoplakia of oral cavity, vulva, and penis

B. Benign neoplasms; examples include
   1. Villous adenoma of the colon
   2. Familial adenomatous polyposis of the colon

HOST DEFENSES AGAINST CANCERS—TUMOR IMMUNITY

A normal function of the immune system is to inspect the body for emerging malignant cells and destroy them, this is referred to as immune surveillance.

Immune Surveillance
The strongest evidence for the existence of immune surveillance is the increased frequency of cancers in immuno-deficient (immuno-compromised) hosts, whether this is congenital or acquired.

1. Congenital immunodeficiencies
   About 5% of such individuals develop cancers, and this is about 200 times the prevalence in normal (immunocomponent) individuals.

2. Acquired immunodeficiencies
   Examples include immunosuppressed transplant recipients and patients with AIDS. Affected individuals have an increased incidence of malignancies. Most (but not all) of these neoplasms are malignant lymphomas. Most cancers, however, occur in persons who do not show any evidence of immunodeficiency. There must be then mechanisms developed by tumor cells to escape or evade the immune system in the immunocompetent hosts.

These mechanisms include

1. Selective outgrowth of antigen-negative tumor cells: during tumor progression, strongly immunogenic subclones may be eliminated by the immune system leaving antigen-negative ones. These, understandably, can not be detected by the immune system.
2. Loss or reduced expression of MHC molecules: tumor cells may fail to express normal levels of HLA class I molecules (which are required for activation of cytotoxic T cells) thereby escaping attack by cytotoxic T cells.
3. Lack of co-stimulation: T-cells requires two signals to be sensitized against cancer cells, one is offered by MHC class I antigenic molecules and the other by co-stimulatory molecules. Failure to express the latter by the tumor cells not only prevents sensitization but also may cause T-cells to undergo apoptosis.
4. **Immunosuppression**: tumor growth factor-β (TGF-β), secreted by many tumors, is a potent immunosuppressant.
5. **Antigen masking**: cell-surface antigens of tumors may be hidden, or masked, from the immune system.
6. **Killing of cytotoxic T cells**: some carcinomas (e.g. melanomas and hepatocellular carcinomas), as a defensive mechanism, kill tumor-specific T lymphocytes that encounter them.

**EFFECTS OF TUMORS ON THE HOST**
Cancers are more aggressive than benign tumors. Nonetheless, both types of neoplasia may cause problems through

1. **Local progression**
Some tumors have critical locations e.g. pituitary adenoma. Although the tumor is benign, its enlargement and expansion can destroy the remaining normal pituitary and thus lead to pan- hypopituitarism. Neoplasms in the GIT (both benign and malignant), may lead to obstructions as they enlarge. The following are examples of tumors can cause outlet obstruction of their respective organs as they enlarge
   1. Carcinoma of esophagus
   2. Carcinoma of gastric pyloric antrum
   3. Carcinoma of small & large intestines
   4. Carcinoma of the head of pancreas, common bile duct, or duodenum leading to obstructive jaundice.
   5. Sometimes, peristaltic movement telescopes the neoplasm and its affected segment into the distal adjacent segment, producing intussusception of the small intestine.

2. **Functional hormonal activity**
Neoplasms arising in endocrine glands may produce manifestations by synthesizing hormones. Such functional activity is more common with benign tumors than with cancers. The latter may be poorly differentiated or undifferentiated to the extent of losing their functional activity i.e. hormone synthesis. A benign β-cell adenoma of the pancreatic islets may produce excessive insulin to cause fatal hypoglycemia. In addition, some nonendocrine tumors may produce hormones or hormone-like substances and give rise to paraneoplastic syndromes (to be described later).

3. **Bleeding and secondary infections**
The destructive growth of cancers or the expansile pressure of a benign tumor on any natural surface, such as the skin, mucosa of the GIT, urinary or respiratory passages, may cause ulcerations, that lead to melena, hematuria, and hemoptysis respectively. Additionally, destruction of these mechanical barriers predisposes to secondary microbial infections.

4. **Acute presentation** may occur in association with tumors; these are caused by for e.g. perforation of the stomach, small or large intestine and spontaneous
rupture or infarction of the tumor itself. The latter is exemplified by torsion of ovarian tumors.  

**Additionally, malignant tumors may be associated with two additional complications**

5. **Cancer cachexia**

This refers to a syndrome of progressive loss of weight accompanied by weakness, anorexia, and anemia that occur frequently in patients with cancer. It may be due to anorexia, tumor parasitism, and the action of soluble factors such as tumor necrosis factor (TNF) produced by the tumor as well as by the host in response to the tumor. In patients with cancer, basal metabolic rate is paradoxically increased despite reduced food intake. This is in contrast to starvation, where there is an adaptational lowering of metabolic rate. Furthermore, in cancer cachexia, there is equal loss of fat and muscle, whereas in starvation the muscle mass is relatively preserved at the expense of fat stores.

6. **Paraneoplastic syndromes**

These refer to the presence of clinical features in patients with cancers that cannot be explained by the physical presence of the malignant neoplasm or its metastases. Excluded from this definition are hormonal features produced by genuine endocrine cell tumors e.g. functioning (thyroxin-producing) follicular carcinoma of the thyroid; in this situation the hormone production is an inherent property of the differentiated malignancy. Paraneoplastic syndromes are important because they

1. are frequent being encountered in 10% of patients with cancer  
2. may be the earliest manifestations of as yet undiscovered (occult) malignancy  
3. may be serious and sometimes fatal  
4. may simulate clinically metastatic disease and as such confuse management

**Some of the more common syndromes are**

1. **Endocrinopathies**

These are frequently encountered paraneoplastic syndromes. Because the cancer cells are not of endocrine origin, this functional activity is referred to as **ectopic hormone production**.

1. **Cushing syndrome** due to secretion of ACTH or ACTH-Like peptides. It is relatively common; almost half of the cases are associated with small cell carcinomas of the lung.
2. **Inappropriate ADH secretion** associated, for e.g. with small cell carcinoma of the lung.
3. **Hypercalcemia** due to the secretion of parathyroid hormone-like substance. It is probably the most common paraneoplastic syndrome. Examples include carcinomas of the breast, lung (especially squamous cell carcinoma), kidney, and ovary. Hypercalcemia due to skeletal metastases is not a paraneoplastic syndrome.
4. Hypoglycemia is due to the secretion of insulin or insulin-like substance e.g. in association with fibrosarcoma and hepatocellular carcinoma.
5. Polycythemia is due to the secretion of erythropoietin as with renal cell carcinoma or hepatocellular carcinoma.

II. The neuromyopathies take diverse forms, such as peripheral neuropathies and a myasthenic syndrome similar to myasthenia gravis. The latter in association with small cell lung carcinoma is referred to as Lambert-Eaton syndrome.

III. Dermatopathies
1. Acanthosis nigricans is due to secretion of epidermal growth factor as with lung and uterine carcinomas. It is characterized by gray-black warty patches of the skin.
2. Dermatomyositis

IV. Hypertrophic osteoarthropathy & clubbing of the fingers are encountered in up to 10% of patients with bronchial carcinomas.

V. Vascular and Hematologic Changes
Migratory thrombophlebitis (Trousseau phenomenon) is due to tumor products (e.g. mucin that activates clotting factors) as with pancreatic and lung carcinomas.
Disseminated intravascular coagulation (DIC) is most commonly associated with some acute leukemias and prostatic adenocarcinoma.
Small, nonbacterial vegetations sometimes form on the cardiac valves, particularly in patients with advanced mucin-secreting adenocarcinomas. The vegetations are potential sources of emboli that can further complicate the course of cancer.
Erythrocytosis is due to erythropoietin production by for e.g. renal cell and liver cell carcinomas.
Autoimmune hemolytic anemia: are seen in association with some leukemias and lymphomas.

VI. Others
Fever: this is likely to be due to pyrogen release (e.g. Hodgkin’s lymphoma, renal cell carcinoma, osteosarcoma).
Nephrotic syndrome (proteinuria, hypoproteinemia and edema): this is seen in various cancers.
Amyloidosis is sometimes associated with multiple myeloma and renal cell carcinoma.
<table>
<thead>
<tr>
<th>Clinical Syndromes</th>
<th>Major Forms of Underlying Cancer</th>
<th>Causal Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENDOCRINOPATHIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Small-cell carcinoma of lung</td>
<td>ACTH or ACTH-like substance</td>
</tr>
<tr>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neural tumors</td>
<td></td>
</tr>
<tr>
<td>Syndrome of inappropriate antidiuretic hormone secretion</td>
<td>Small-cell carcinoma of lung; intracranial neoplasms</td>
<td>Antidiuretic hormone or atrial natriuretic hormones</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Squamous cell carcinoma of lung</td>
<td>Parathyroid hormone–related protein (PTHRP), TGF-α, TNF, IL-1</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult T-cell leukemia/lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Ovarian carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrosarcoma</td>
<td>Insulin or insulin-like substance</td>
</tr>
<tr>
<td></td>
<td>Other mesenchymal sarcomas</td>
<td></td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchial adenoma (carcinoid)</td>
<td>Serotonin, bradykinin</td>
</tr>
<tr>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Gastric carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal carcinoma</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td></td>
<td>Cerebellar hemangioma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>NERVE AND MUSCLE SYNDROMES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Bronchogenic carcinoma</td>
<td>Immunological</td>
</tr>
<tr>
<td>Disorders of the central and peripheral nervous system</td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>DERMATOLOGIC DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Clinical Syndromes

<table>
<thead>
<tr>
<th>Clinical Syndromes</th>
<th>Major Forms of Underlying Cancer</th>
<th>Causal Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
<td>Gastric carcinoma</td>
<td>Immunological; secretion of epidermal growth factor</td>
</tr>
<tr>
<td></td>
<td>Lung carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uterine carcinoma</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Bronchogenic, breast carcinoma</td>
<td>Immunological</td>
</tr>
</tbody>
</table>

#### OSSEOUS, ARTICULAR, AND SOFT-TISSUE CHANGES

| Hypertrophic osteoarthropathy and clubbing of the fingers | Bronchogenic carcinoma | Unknown |

#### VASCULAR AND HEMATOLOGIC CHANGES

<table>
<thead>
<tr>
<th>Venous thrombosis (Trousseau phenomenon)</th>
<th>Pancreatic carcinoma</th>
<th>Tumor products (mucins that activate clotting)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bronchogenic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other cancers</td>
<td></td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
<td>Advanced cancers</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td></td>
<td>Thymic neoplasms</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### OTHERS

| Nephrotic syndrome                     | Various cancers      | Tumor antigens, immune complexes              |

#### GRADING AND STAGING OF CANCERS

To assess prognosis (the likely outcome of a disease) & effectiveness of various forms of treatment, malignant tumors should be separated into different groups; each of which includes members that simulate each other in respect to certain microscopic & biologic properties. To achieve this, systems have been developed to express the degree of differentiation (grade) and extent of cancer spread (stage). Both grade and stage reflect the level of aggressiveness of various neoplasms.

**Grading**

Microscopic features that seem to influence the expected behavior of cancers are the grade, number of mitoses, and presence or absence of foci of necrosis; these features are inter-related. Cancers are classified into four grades (1 to 4) with increasing anaplasia i.e. G1 for well-differentiated; G2 for moderately-differentiated, G3 for poorly-differentiated and G4 for undifferentiated cancers. Studies have shown that grading of cancers is of less clinical value than staging.
Staging

The staging of cancers is based on
1. The size of the primary cancer
2. Its extent of spread to regional lymph nodes, and
3. The presence or absence of blood-borne metastases

Two major staging systems are currently in use, one developed by the Union Internationale Contre Cancer (UICC) (International union against cancer) and the other by the American Joint Committee (AJC). The UICC classification is referred to as the TNM system—T for primary tumor, N for regional lymph node involvement, and M for metastases. This TNM staging varies for each specific form of cancer, but there are general principles: with increasing size, the primary cancer is described as T1 to T4. Sometimes the T refers to the depth of invasion (not the size) as in GIT carcinomas. TIS indicates an in situ cancer.

N0 would mean no nodal involvement, whereas N1 to N3 would indicate involvement of an increasing number and range of lymph nodes. M0 signifies no distant metastases, whereas M1 (or sometimes M2) indicates the presence of blood-borne metastases. Example: breast carcinoma, 3 cm in maximal dimension, with axillary lymph node metastases on the same side of the cancer, but with no distant metastases would be T2 N1 M0. (Fig. 8-24)

Staging of neoplastic diseases is of great importance in predicting prognosis and in the selection of the best form of therapy for the patient and has proved to be of greater clinical value than grading. However, the two are generally correlated in that tumors of high grade present at high stage, while tumors of low grade present at low stage.

LABORATORY DIAGNOSIS OF CANCER

There are several approaches to the correct pathological diagnosis of cancer and sometimes more than one approach is employed.

A. Histologic and Cytologic Methods

Separating benign from malignant neoplasms is usually not difficult by these two methods. However, care should be taken in diagnosing a group of tumors that lay in the middle of the spectrum i.e. in the gray zone; these are designated as borderline tumors. Cooperation between the clinician and the pathologist facilitates greatly the achievement of the correct diagnosis. Clinical data and surgical findings during the operation are helpful for optimal pathologic diagnosis.

Surgical specimens delivered to the lab as far as tumor diagnosis is concerned should be
1. Adequate
2. Representative of the lesion
3. Properly preserved in a fixative; routinely formalin

Samples delivered for pathological evaluation may represent:
1. Incisional or excisional biopsy specimen for
   a. conventional histopathological diagnosis
   b. frozen section diagnosis
2. Needle Biopsies
   a. Fine needle aspiration material (cytology)
   b. Needle-core biopsy material (histopathology)
3. Endoscopic biopsy material
4. Laparoscopic, or thoracoscopic biopsies
5. Cytologic smears from the tumor in question

1. **Incisional biopsy** means that only a portion of the lesion is sampled, and therefore the procedure is strictly of a diagnostic nature. In **excisional biopsies**, the entire lesion is removed, usually with a rim of normal tissue, and therefore the procedure serves both a diagnostic and a therapeutic function. When excision of the whole lesion is not possible, incisional biopsy is performed, however, selection of an appropriate site for a biopsy of a large mass by the surgeon requires awareness that the margins of the lesion may not be representative and its center may be largely necrotic. Requesting an intraoperative "quick-frozen section" diagnosis is sometimes desirable, for example, in determining the nature of a mass lesion or in evaluating the margins of an excised cancer to ascertain that the entire neoplasm has been removed. This method permits histologic evaluation within minutes, while the patient is still under anesthesia. The results in such cases will modify the course of the surgical operation.

2. **Needle biopsies**
   **Fine-needle aspiration** of tumors
   During fine-needle aspiration, a long, thin needle is inserted into the suspicious area. A syringe is used to draw out fluid and cells for analysis. The material is then spread on a slide, stained and then examined for the evaluation of the mass.
   **Core needle biopsy**
   A wide-bore needle with a cutting tip is used to draw a thin core of tissue (the size of a match stick) out of a suspicious area. The tissue obtained is processed to obtain histological sections for evaluation. **Image-guided biopsy** combines an imaging procedure, such as X-ray, computerized tomography (CT) or ultrasound, with a needle biopsy. Image-guided biopsy allows access to suspicious areas that cannot be felt through the skin, such as a suspicious lesion of the liver or prostate. Through the use of images, it possible to be sure that the biopsy needle reaches the correct spot.

3. **Endoscopic biopsies**
   During endoscopy, a thin, flexible tube with a light on the end (endoscope) is used to see structures inside the body. Special tools are passed through the tube to take small samples of tissue for pathological analysis. Tubes used in an
endoscopic biopsy can be inserted through the mouth, rectum, urethra (transurethral), etc. Examples of endoscopic biopsy procedures include:
- Cytoscopy to collect biopsies from inside the urinary bladder,
- Bronchoscopy to get tissue from bronchial/lung structures and
- Gastroscopy or colonoscopy to collect tissues from the stomach or colon respectively

4. **Laparoscopy, Thoracoscopy, and Mediastinoscopy**

Laparoscopy is similar to endoscopy but is used to look inside the abdominal cavity and remove tissue samples. A small incision is made in the abdomen, then the laparoscope is passed through this opening to see the inside. Similar procedures to look inside the chest are called thoracoscopy and mediastinoscopy.

5. **Cytology**

Diagnosing diseases based on looking at single cells and small clusters of cells is called cytology or cytopathology. It has become more important in cancer diagnosis over the past few decades. Sometimes, as in some fine needle aspiration (FNA) samples, only one drop of blood or tissue fluid (containing tiny fragments of the tumor) is taken. On the other hand, some pleural fluid or peritoneal fluid cytology samples may include large amount of fluid. In the latter case, a sample (e.g. 5 ml) is taken and centrifuged. The deposit is taken and spread on a glass slide and then stained and screened under the microscope for malignant cells. **Diagnostic cytology, when performed by well-trained, experienced individuals, offers an extremely high degree of reliability.**

B. **Histochemistry**

The basis of surgical pathology is the examination of the specimens following fixation in formalin, processing in graded alcohols and xylene, embedding in paraffin, cutting of sections with a microtome, and staining with hematoxylin-eosin (H&E). This technique gives a lot of information quickly with a little cost. That is why it is the standard method in all histopathology labs.

In the H&E technique, hematoxylin staining of nuclei is followed by counterstaining of cytoplasm and various extracellular materials by eosin. However, sometimes, H&E staining of sections is not enough for establishing a final decisive diagnosis. Several stains are available that react chemically with certain constituents of the neoplastic cells to give a colored reaction that highlights a specific feature that would otherwise unclear with the H&E stain. (e.g., presence of mucins in adenocarcinoma, melanin in amelanotic melanoma, striations in rhabdomyosarcoma, glial fibers in gliomas, etc.). These stains are called **special stains** (because they are employed under special circumstances). Currently, a small minority of these special stains are of real diagnostic utility. This is especially true since the advent of immunohistochemistry, which renders many of these special stains out of date.
C. Immunohistochemistry (IHC)
This is the application of immunologic principles & techniques to the study of cells & tissues. The availability of specific monoclonal antibodies has greatly facilitated the identification of cell products or cell surface markers. In several situations, the differentiation between neoplasms may be very difficult for e.g. with the anaplastic large cell malignancies; even the most experienced pathologists cannot tell whether the submitted tumor is a squamous cell carcinoma, adenocarcinoma, lymphoma or a sarcoma. Differentiation between these is of prognostic & therapeutic implications. It is through the application of a panel of specific monoclonal antibodies, which disclose the presence or absence of certain products or cell markers in these cells, so that the more specific, final diagnosis can be reached. Examples of the utility of immunohistochemistry in the diagnosis or management of malignant neoplasms include
1. Categorization of undifferentiated malignant tumors
2. Categorization of leukemias and lymphomas
3. Determination the site of origin of metastatic tumors
4. Detection of molecules that have prognostic or therapeutic significance

D. Serum Tumor Markers
Tumor markers are either substances released by cancer cells into the blood (or urine) or substances created by the body in response to cancer cells. They include cell-surface antigens, cytoplasmic proteins, enzymes, and hormones. In clinical practice, a tumor marker usually refers to a molecule specific to a particular neoplasm that can be detected in the plasma or other body fluids. Their main utility is a laboratory test to
1. support the diagnosis of cancer
2. to determine the response to therapy
3. to indicate recurrence during the follow-up period.
Some of these tumor markers can also be detected imunohistochemically in tissue sections (see above). A host of tumor markers has been described, and new ones are identified every year. Examples include:
Carcinoembryonic antigen (CEA) is a complex glycoprotein that is elaborated by many different neoplasms. Its serum levels are reported to be positive in colorectal, pancreatic, gastric and breast carcinomas. In patients with CEA-positive colon carcinomas, the persistence of elevated CEA levels 6 weeks after surgical removal indicates a residual (left behind) tumor tissues, whereas a rising CEA levels indicates recurrence.
α-fetoprotein (AFP) is another well-established tumor marker. AFP levels have proved to be a useful indicator of hepatocellular carcinomas and germ cell tumors of the testis or ovary. AFP levels decline rapidly after surgical resection of liver cell cancer or treatment of germ cell tumors of the testis. Serial post-therapy measurements of AFP levels in patients with germ cell tumors of the testis provide a sensitive index of response to therapy and recurrence.
**Prostate-specific antigen (PSA)**

An elevated PSA level in the blood may indicate prostate cancer, but other conditions such as benign prostatic hyperplasia (BPH) and even prostatitis can also raise PSA levels. PSA levels are used also to evaluate how a patient has responded to treatment and to check for tumor recurrence.

The development of tests to detect cancer markers in blood and body fluids is an active area of research.

**Ca-125** is a glycoprotein expressed by coelomic epithelium during fetal development. Increased serum levels can be present in patients with ovarian cancer. Other malignancies such as pancreatic carcinoma may also have increased levels. Non malignant causes of high serum Ca125 include pregnancy, endometriosis and liver failure.

**D. Electron microscopy:**

The main use of diagnostic electron microscopy is involved not with the question of whether a tumor is malignant or not, but with the issue of tumor classification. Cytoplasmic organelles such as melanosomes are indicative of melanocytic lesions such as malignant melanoma, the presence of desmosomes points to an epithelial tumor (carcinoma), and structures such as myosin and actin filaments arranged in "Z" bands are indicative of skeletal muscle differentiation and hence if found in a tumor would suggest a rhabdomyosarcoma. Neurosecretory dense core granules are found in tumors with neuroendocrine differentiation.

Several other relatively recent & sophisticated techniques are employed in both the diagnosis of & researches on neoplasia. These are beyond the scope of this lecture; the interested student can look them up in the specialized text books, examples of these include

**E. Flow Cytometry** is a technique used to measure individual cell characteristics such as membrane antigens and DNA content of tumor cells. The classification of leukemias and lymphomas is based on cell surface antigens which can be easily identified by flow cytometry. DNA ploidy appears to correlate with prognosis in a variety of tumors. In general, aneuploidy seems to be associated with a poorer prognosis in early-stage breast cancer, bladder, lung, colorectal and prostate cancer.

**F. Molecular techniques** such as polymerase chain reaction (PCR), the Southern blot analysis of DNA and the Northern blot analysis of RNA are used in tumor diagnosis.

**G. DNA microarray analysis**

**H. Tissue microarrays analysis**