Underwood: Chapter 10: Tumours: Benign and Malignant

Definition of Tumours

The word *tumour* means literally an abnormal swelling. *A tumour (neoplasm) is defined as a lesion resulting from the autonomous or relatively autonomous abnormal growth of cells which persists after the initiating stimulus has been removed; i.e., cell growth has escaped from normal regulatory mechanisms.* Tumours are the result of transformation of any single nucleated cell in the body, although some cell types are more prone to tumour formation than others. Such lesions usually form swellings, but they are not the only cause of abnormal swellings.

The term *neoplasm* (new growth) is synonymous with the medical meaning of the word tumor and is often used in preference because it is less ambiguous and not quite so alarming for patients. *Cancer* is a word used more in the public arena than in medicine; it has emotive connotations and generally refers to a malignant tumour or neoplasm.

Incidence of Tumours

Malignant neoplasms develop in approximately 25% of the population in the UK. Cancer accounts for about one-fifth of all deaths in developed countries. Lung cancer is the most frequently occurring single malignant neoplasm in the UK and USA.

Structure of Tumours

Solid tumours consist of neoplastic cells and stroma. The neoplastic cell population reproduces to a variable extent the growth pattern and synthetic activity of the parent cell of origin.

Stroma

The neoplastic cell population is embedded in an supported by a connective tissue framework called the stroma (from the Greek word meaning a mattress), which provides mechanical support and nutrition to the neoplastic cells. The process of stroma formation is called a desmoplastic reaction and may be due to induction of connective tissue proliferation by growth factors in the immediate tumour environment.

Tumour stroma always contains blood vessels which perfuse the tumour. This vascular proliferation is thought to be induced by an angiogenic factor produced by the tumour cells.

Fibroblasts offer some mechanical support for the tumour cells and may in addition have nutritive properties. Stromal myofibroblasts are often abundant, particularly in scirrhous carcinomas of the breast; their contractility is responsible for the puckering and retraction of adjacent structures.

The stroma often contains a lymphocytic infiltrate of variable density.

Tumour Shape and Texture

The gross appearance of a tumour may be described as sessile, papillary, polypoid, fungating, ulcerated or annular.

Ulcerated tumours can often be distinguished from non-neoplastic ulcers, such as peptic ulcers in the stomach, because the former tend to have heaped-up or rolled edges.

Tumours are usually firmer than the surrounding tissue, causing a palpable lump in accessible sites such as the breasts. Extremely hard tumours are referred to as 'scirrhous'. Softer lesions are sometimes called 'medullary'; they occur in the thyroid and breasts.

Classification of Tumours

- Behavioural classification: benign or malignant

- Histogenetic classification: cell of origin

- Precise classification of individual tumours is important for planning treatment.

Some tumours, such as those of the ovary, defy precise behavioural classification, because their histology is intermediate between that associated with benign and malignant tumours; these are ofter referred to as 'borderline' tumours.

Benign Tumours

- Non-invasive and remain localised

- Slow growth rate

- Close histological resemblance to parent tissue.

When a benign tumour arises in an epithelial or mucosal surface, the tumour grows away from the surface, because it cannot invade, often forming a *polyp* which may be either pedunculated (stalked) or sessile; this non-invasive outward direction of growth gives rise to an *exophytic* tumour.

They may cause clinical problems due to:

- pressure of adjacent tissues (i.e., benign meningeal tumour causing epilepsy)

- obstruction of the flow of fluid (i.e., benign epithelial tumour arising in a duct)

- production of a hormone (i.e., benign thyroid tumour causing thyrotoxicosis

- anxiety.

Malignant Tumours

- Invasive and thus capable of spreading directly or by metastasis

- Relatively rapid growth rate

- Variable histological resemblances to the parent tissue.

The invasive inward direction of growth gives rise to an *endophytic* tumour.

The considerable morbidity and mortality associated with malignant tumours may be due to:

- pressure on and destruction of adjacent tissue

- formation of secondary tumours (metastases)

- blood loss from ulcerated surfaces

- obstruction of flow

- production of a hormone (i.e., ACTH and ADH from some lung tumours)

- other paraneoplastic effects causing weight loss and debility

- anxiety and pain.

Histogenesis

Histogenesis - the specific cell of origin of an individual tumour - is determined by histopathological examination and specifies the tumour *type.*

Differentiation

The term *differentiation* means the degree to which the tumour resembles histologically its cell or tissue of origin; it determines the tumour *grade.*

Nomenclature of Tumours

- All have the suffix '-oma'

- Benign epithelial tumours are either papillomas or adenomas

- Benign connective tissue tumours have a prefix denoting the cell of origin

- Malignant epithelial tumours are carcinomas

- Malignant connective tissue tumours are sarcomas.

A tumour that defies accurate classification is designated anaplastic; such tumours are always malignant.

Epithelial Tumours

Benign Epithelial Tumours

- *papilloma*

- *adenomas.*

A *papilloma* is a benign tumour of non-glandular or non-secretory epithelium, such as transitional or stratified squamous epithelium. An *adenoma* is a benign tumour of glandular or secretory epithelium.

Malignant Epithelial Tumours

Malignant tumours of epithelium are always called *carcinomas.* Carcinomas of non-glandular epithelium are always prefixed by the name of the epithelial cell type. Malignant neoplasms of glandular epithelium are always deisgnated *adenocarcinomas,* coupled witth the name of the tissue of origin.

Carcinoma In Situ

The term *carcinoma in situ* refers to an epithelial neoplasm which has all the cellular features associated with malignancy, butt which has not yet invaded through the epithelial basement membrane separating it from potential routes of metastasis - blood vessels and lymphatics. Detection of CIS, or of their precursor lesions, is the aim of population screening programmes for cervical and some other carcinomas. The phase of CIS growth may last for several years before invasion commences.

CIS may be preceded by a phase of dysplasia, in which the epithelium shows disordered differentiation short of frank neoplasia. Some dysplastic lesions are almost certainly reversible. As there is ambiguity in the use of the word 'dysplasia' as well as some difficulty in consistently distinguishing between CIS and dysplasia in biopsies, the term is now less favoured. The term 'intra-epithelial neoplasia', as in cervical intra-epithelial neoplasia (CIN), is used to embrace both CIS and the precursor lesions formerly known as dysplasia.

Connective Tissue and Other Mesenchymal Tumours

Benign Connective Tissue and Mesenchymal Tumours

- *lipoma:* benign tumour of the lipocytes of adipose tissue

- *rhabdomyoma:* benign tumour of striated muscle

- *leiomyoma:* benign tumour of smooth muscle

- *chondroma:* benign tumour of cartilage

- *osteoma:* benign tumour of bone

- *angioma:* benign vascular tumour.

Malignant Connective Tissue and Mesenchymal Tumours

Malignant tumours of mesenchyme are always designated *sarcomas* prefixed by the name that describes the cell or tissue of origin. Examples include:

- *liposarcoma:* malignant tumour of lipocytes

- *rhabdomyosarcoma:* malignant tumour of striated muscle

- *leiomyosarcoma:* malignant tumour of smooth muscle

- *chondrosarcoma:* malignant tumour of cartilage

- *osteosarcoma:* malignant tumour of bone

- *angiosarcoma:* malignant vascular tumour.

Eponymously Named Tumours

- *Burkitt's lymphoma:* a B-cell lymphoma associated with the Epstein-Barr virus and endemic in certain parts of Africa

- *Ewing's sarcoma:* a malignant tumour of bone of uncertain histogenesis

- *Grawitz tumour:* a carcinoma of renal tubular epithelium, now more commonly called hypernephroma or clear-cell carcinoma of the kidney

- *Kaposi's sarcoma:* a malignant neoplasm possibly derived from vascular endothelium, now commonly associated with AIDS.

Miscellaneous Tumours

Teratomas

A teratoma is a neoplasm characterised by the presence of cells representing all three germ cell layers: ectoderm, mesoderm and endoderm. The tumour may contain teeth and hair, and histological evidence of respiratory epithelium, cartilage, muscle, neural tissue, etc. In their malignant form, these representatives of ectoderm, mesoderm and endoderm will be less easily identifiable.

Teratomas are considered to be of germ-cell origin. They occur most often in gonads, where germ cells are abundant. Although all cells in the body contain the same genetic information, it is perhaps in the germ cells that this information is in the least repressed state and is therefore capable of programming such divergent lines of differentiation. Supporting evidence for a germ-cell origin for teratomas comes from karyotypic analysis of their sex chromosome content. Teratomas in the female are always XX, whereas only 50% of those in the male are XX and the remainder XY; this correlates with the sex chromosome distribution in the germ cells of the two sexes.

Ovarian teratomas are almost always benign and cystic; in the testis, they are almost always malignant and relatively solid. As germ cells in the embryo originate at a site remote from the developing gonads, teratomas arise occasionally elsewhere in the body, usually in the midline, possibly from germ cells that have been arrested in their migration. These extragonadal sites for teratomas include the mediastinum and sacro-coccygeal region.

Embryonal Tumours: The 'Blastomas'

Some types of tumour occur almost exclusively in the very yound, usually in those below 5 years of age, and bear a histological resemblance to the embryonic form of the organ in which they arise. Examples include:

- *retinoblastoma,* which arises in the eye and for which there is an inherited predisposition

- *nephroblastoma or Wilms' tumour,* which arises in the kidney

- *neuroblastoma,* which arises in the adrenal medulla or nerve ganglia and occasionally 'matures' into a harmless benign ganglioneuroma

- *hepatoblastoma,* which arises in the liver.

Mixed Tumours

Mixed tumours show a characteristic combination of cell types. The best example is the mixed parotid tumour (pleomorphic salivary adenoma); this consists of glands embedded in a cartilaginous or mucinous matrix thought to be derived from the myoepithelial component of the gland. Another common mixed tumour is the fibroadenoma of the breast, a lobular tumour consisting of epithelium-lined glands or clefts in a loose fibrous tissue matrix.

The occurrence of mixed tumours in an individual organ can sometimes be predicted from its embryology. This is illustrated by the Mullerian tract tumors that occur in the female genital tract; these often contain a mixture of carcinomatous and sarcomatous elements reflecting the innate capacity of the tissue for divergent differentiation.

A tumour may also have a mixed appearance because of metaplasia within it. For example, transitional carcinomas of the bladder sometimes exhibit foci of glandular or squamous differentiation.

APUDomas and Carcinoid Tumours

APUD (*A*mine Content and/or *P*recursor *U*ptake and *D*ecarboxylation) is the acronym used to describe the cells of the diffuse endocrine system, such as the calcitonin-producing 'C' cells of the thyroid gland, the cells of the islets of Langerhans, and the argentaffin and argyrophil cells of the lungs and the gastrointestinal tract. The APUD acronym describes their histochemical properties, which correlate both with these cells' ability to synthesise peptide hormones and with their content of either 5-hydroxytryptamine or 5-hydroxytryptophan. Tumours derived from these cells are called collectively *APUDomas.*

APUDomas of the gut and respiratory tract that do not produce any known peptide hormone are called *carcinoid tumours.* The appendix is the commonest site, but, here, these tumours are usually an incidental finding of little clinical significance. Carcinoids arising elsewhere (the small bowel is the next commonest site) often metastasise to mesenteric lymph nodes and the liver. Extensive metastases lead to the carcinoid syndrome (tachycardia, sweating, skin flushing, anxiety and diarrhoea) due to extensive production of 5-hydroxytryptamine and prostaglandins.

APUDomas often pursue an indolent course, growing relatively slowly and metastasising late. Their behaviour cannot always be predicted from their histological features.

Some individuals have an inherited familial predisposition to develop APUDomas; they are said to have a multiple endocrine neoplasia (MEN) syndrome.

Insulinoma	Episodes of hypoglycaemia
Gastrinoma	Extensive peptic ulcerations of the upper gut (Zollinger-Ellison syndrome)
Phaeochromocytoma	Paroxysmal hypertension
Carcinoid	If metastases are present, flushing, palpitations and pulmonary valve stenosis

Carcinosarcomas

These are very rare tumours which appear to consist of separate carcinomatous and sarcomatous components. Some may arise from carcinogenic events simultaneously affecting adjacent epithelial and mesenchymal cells. Others may be the result of collision of a coincidentally arising carcinoma and sarcoma.

Hamartomas

A hamartoma is a tumour-like lesion, the growth of which is coordinated with the individual; it lacks the autonomy of a true neoplasm. Hamartomas are always benign and usually consist of two or more mature cell types normally found in the organ in which the lesion arises. A common example occurs in the lung, where a hamartoma typically consists of a mixture of cartilage and bronchial-tyoe epithelium (the so-called 'adenochondroma').

Pigmented naevi or 'moles' may also be considered as hamartomatous lesions. Their clinical importance is two-fold: hamartomas may be mistaken for malignant neoplasms; and hamartomas are sometimes associated with clinical syndromes, as, for example, in tuberose sclerosis.

Cysts

A cyst is a fluid-filled space lined by epithelium. Cysts are not necessarily tumours or neoplasms but, because they may have local effects similar to those produced by true tumors, it is pertinent to consider them here. Common types of cysts are:

- *congenital* (i.e., branchial and thyroglossal cysts) due to embryological defects

- *neoplastic* (i.e., cystadenoma, cystadenocarcinoma, cystic teratoma)

- *parasitic* (i.e., hydatid cysts due to *Echinococcus granulosus*)

- *retention* (i.e., epidermoid and pilar cysts of the skin)

- *implantation* (i.e., as a result of surgical or accidental implantation of epidermis).

The only type of cyst whose aetiology merits its inclusion within this chapter is the neoplastic cyst. This is seen most commonly in the ovary, where it may be either a benign cystic teratoma, filled with sebaceous material, or a cystadenoma or cystadenocarcinoma, each of which may be filled with either serous fluid or mucus depending on the secretory properties of the lining epithelium.

Invasion and Metastasis

- Invasion is the most important sole criterion for malignancy

- Invasion is due to abnormal cell motility, reduced cellular cohesion, and production of proteolytic enzymes

- Metastasis is the process of formation of distant secondary tumours

- Common routes of metastasis include lymphatic channels, blood vessels, and through body cavities.

Invasion

The invasiveness of malignant neoplasms is determined by the properties of the neoplastic cells within them. Factors influencing tumour invasion are:

- abnormal or increased cellular motility
- secretion of proteolytic enzymes
- decreased cellular adhesion.

Cellular motility is abnormal in that the cells are not only more motile than their normal counterparts (which may not move at all), but also show loss of the normal mechanism that arrests or reverses normal cellular migration: contact inhibition of migration.

Neoplastic cells also secrete enzymes, such as collagenase, which cause dissolution of adjacent connective tissue boundaries. Invasion often occurs along tissue planes offering less resistance to tumour growth, such as perineural spaces and, of course, vascular lumina. Other tissues are extremely resistant to neoplastic invasion, such as cartilage and the fibrocartilage of intervertebral discs. Cartilage appears to contain factors that inhibit tumour vascularisation and is therefore a hostile environment.

Invasion is the single most important criterion of malignancy. Metastasis is a consequence, and thus a manifestation, of invasion. In epithelial tumours, invasion is relatively easy to recognise because the basement membrane serves as a clear line of demarcation between the tissue boundaries. In connective tissue tumours, invasion is less easy to recognise unless there is clear evidence of vascular or lymphatic permeation; other histological features, such as mitotic activity, are usually taken into consideration for prognostic purposes.

Invasion within epithelium is known as *pagetoid infiltration;* it is named after Paget's disease of the nipple, which is due to infiltration of the epidermis of the nipple by tumour cells from a ductal carcinoma in the underlying breast. This route of infiltration can also occur with a few other epithelial malignancies.

Metastasis

Metastasis is the process whereby malignant tumours spread from their site of origin (the *primary tumour*) to form other tumours (*secondary tumours*) at distant sites. The total tumour burden resulting from this process can be very great indeed, and the total mass of the secondary tumours invariably exceeds that of the primary lesion; it is not uncommon at autopsy to find a liver weighing several kilograms more than normal, laden with metastases. The word *carcinomatosis* is used to denote extensive metastatic disease.

Sometimes, metastases can be the presenting clinical feature. Bone pain or fractures due to skeletal metastases can be a manifestation of a clinically occul internal malignancy. Palpable lymph nodes, due to metastatic involvement, may appear before the signs and symptoms of the primary tumour.

The cells of a malignant neoplasm are capable of metastasising because they can invade into potential routes of dissemination, such as blood vessels and lymphatics. The cells are also less cohesive than those of their normal or benign counterparts and can therefore easily become detached from the main tumour. The cells also appear to be less site-dependent in their growth requirements.

The routes of metastasis are:

- *haematogenous,* by the blood stream, to form secondary tumours in organs perfused by blood which has drained from a tumour

- *lymphatic,* to form secondary tumours in the regional lymph nodes

- *transcoelomic,* in pleural, pericardial and peritoneal cavities where this invariably results in a neoplastic effusion

- *imlantation,* for example by accidental spillage of tumour cells during the course of surgery.

Carcinomas tend to favour lymphatic spread, while sarcomas favour haematogenous spread. However, exceptions to these tendencies are common, and carcinomas can often give rise to blood-borne metastases.

Haematogenous Metastasis

Bone is a site favoured by haematogenous metastases from five carcinomas - lung, breast, kidney, thyroid and prostate. Other organs commonly involved by haematogenous metastases are lung, liver and brain. The metastases are frequently multiple, whereas primary tumours arising in the affected organs are usually solitary. Curiously, tumours rarely metastasise to skeletal muscle or to the spleen, despite their lavish blood supply.

Metastases reaching the surface of the liver often have a central depression ('umbilication') as a consequence of necrosis within the tumour nodule.

Lymphatic Metastasis

Tumour cells reach the lymph node through the afferent lymphatic channel. The tumour cells settle and grow in the periphery of the node, gradually extending to replace it. Lymph nodes involved by metastatic tumours are usually firmed and larger than normal. Groups of involved lymph nodes may be matted together by both tumour tissue and the connective tissue reaction to it. Lymph node metastases often interrupt lymphatic flow, thus causing oedema in the territory that they drain.

Transcoelomic Metastasis

The peritoneal, pleural and pericardial cavities are common sites of transcoelomic metastasis, which results in an effusion of fluid into the cavity. The fluid is rich in protein (i.e., it is an exudate) and may contain fibrin. The fluid also contains the neoplastic cells causing the effusion, and cytological examination of the aspirated fluid is very important in diagnosing the cause of effusions into body cavities. The tumour cells often grow as nodules on the mesothelial surface of the cavity.

Peritoneal effusions (ascites) may be due to involvement by any abdominal tumour, but primaries within the ovaries are particularly common. Pleural and pericardial effusions are common consequences of carcinomas of the breasts and lungs.

Biology of Tumour Cells

- No single biological feature is unique to neoplastic cells

- Neoplastic cells are relatively or absolutely autonomous, unresponsive to extracellular growth control

- Neoplastic cells frequently have quantitative and qualitative abnormalities of DNA

- Tumour products include fetal substances and unexpected hormones.

Contrary to past claims and an enduring hope, there is no single feature unique to neoplastic cells other than the general property of relative or absolute autonomy. Many of the other features of tumours have normal counterparts: mitotic activity is a feature also of regenerating cells; placental trophoblast is invasive; and the nucleated cells of the blood and lymph wander freely around the body, settling in other sites.

Tumours result from the *clonal proliferation* of a single cell following a carcinogenic stimulus. Because the proliferative effect persists after withdrawal of the stimulus and is inherited by subsequent generations of cells, it follows that the molecular lesion resulting in neoplastic growth is within the genome.

One of the many difficulties in studying tumours is their genetic instability, leading to the formation of many clones within one tumour. This is often reflected in the histology which may show a heterogenous growth pattern, some areas appearing better differentiated than others. Clinically, this instability and consequent heterogeneity is important because it enables tumours to resist chemotherapy; consequently, many chemotherapeutic regimes employ a combination of agents administered simultaneously or sequentially.

DNA of Tumour Cells

Tumour cells have abnormal nuclear DNA. The total amount of DNA per cell commonly exceeds that of the normal diploid (2N) population. This is evident in histological sections as *nuclear hyperchromaticism.* The amount of DNA may appear to increase in exact multiplies of the diploid state (polyploidy) such as tetraploid (4N) and octaploid (8N); alternatively there may be aneuploidy, the presence of inexact multiples of DNA per cell.

Aneuploidy and polyploidy are associated with increased tumour aggressiveness and are recognisable in histological sections as variations in nuclear size and staining (*pleomorphism*).

At a chromosomal level these abnormalities of DNA are associated with the presence of additional chromosomes and with chromosomal translocations. A very few of these *karyotypic abnormalities* have a regular association with specific tumours; the best known and one of the most consistent is the association of the Philadelphia chromosome with chronic myeloid leukaemia.

Genetic Abnormalities in Tumours

Genetic abnormalities are being discovered with increasing frequency in tumours. Some of these may be relatively late events, epiphenomena with no central role in the cancer process. However, others may be of fundamental importance, appearing at an early stage in the development of the tumour. Oncogenes are of considerable interest in this regard because of their possible involvement in carcinogenesis.

Mitotic Activity and Cellular Proliferation

Malignant tumours frequently appear to exhibit more mitotic activity than the corresponding normal cell population. In histological sections, mitoses are abundant, and mitotic figures are often grossly abnormal showing tripolar and other bizarre arrangements. It is likely that these aberrant mitoses are incapable of proceeding to completion. Cellular proliferation can be estimated by mitosis counting, DNA measurements and other techniques.

Perhaps as important as the increased mitotic activity is cell loss in tumours through ischaemic and apoptotic necrosis; the latter is a common finding in slow growing tumours with a high mitotic rate (i.e., basal cell carcinoma of the skin). The growth rate of a tumour is the balance between cellular proliferation and loss.

Metabolic Abnormalities in Tumours

Although many tumours show a tendency towards *anaerobic glycolysis*, there are no metabolic abnormalities entirely specific to the neoplastic process. The known metabolic abnormalities of tumour cells are simply inappropriate to the normal physiological state of the tissue or host.

The surface of tumours cells is abnormal. Tumour cells have a greater *negative surface charge* than do normal cells, and are also less cohesive. In epithelial neoplasms, poor cellular cohesion is also due to a reduction in specialised intercellular junctions such as desmosomes. These changes may explain the ease with which malignant tumour cells spread through tissues and detach themselves to populate distant organs.

Tumour cells may retain the capacity to synthesise and secrete products characteristic of the normal cell type from which they derived, often doing so in an excessive and uncontrollable manner. In addition, tumours often show evidence of *gene depression.* All somatic cells contain the same genetic information, but only a small proportion of the genome is transcribed into RNA and translated into protein in any normal cell. Most genes are repressed, and only those required for the function of the particular cell are selectively expressed. However, in many tumour cells, genes become *depressed*, resulting in the inappropriate synthesis of unexpected substances.

Tumour Products

The major types of tumour products are:

- substances appropriate to their cell of origin (i.e., keratin from a squamous cell carcinoma, steroid hormones from an adrenocortical adenoma)

- substances inappropriate or unexpected for their cell of origin (i.e., ACTH and ADH from oat-cell carcinomas of the lung)

- fetal reversion substances (i.e., carcinoembryonic antigen from adenocarcinomas of the gastrointestinal tract, alpha-fetoprotein from liver cell carcinomas and testicular teratomas)

- substances required for growth and invasion (i.e., autocrine growth factors, angiogenic factors, collagenases).

Some tumour products are useful as markers for diagnosis or follow-up. They can be detected in histological sections or their concentrations measured in the blood. Rising blood levels suggest the presence of tumour; falling levels indicate a sustained response to therapy.

Growth Factors, Hormones and Their Receptors

The single major difference between neoplastic cells and their normal or reactive counterparts is that the former are autonomous with respect to their growth control. Whereas normal cells require extracellular signals for their growth and the induction of some functions, neoplastic cells behave independently of this mechanism.

Neoplastic cells sustain their growth either by producing growth factors for which they already have receptors, or by producing receptors for growth factors already present in the cellular environment. The process is known as *autocrine control.* Many oncogenes, frequently found to be abnormally expressed in neoplastic cells, encode for some growth factors, their receptors, or closely related molecules.

The autonomy of neoplastic cells is often relative rather than absolute. For example, approximately two-thirds of breast carcinomas retain the capacity to synthesise oestrogen receptors; these tumours are better differentiated than receptor-negative breast carcinomas and they have a better prognosis. Furthermore, if women with oestrogen-receptor-positive breast carcinomas are given tamoxifen (a drug which blocks the receptor) or have their ovaries removed surgically (which removes the major source of oestrogens) they survive longer than women with receptor-positive tumours who have not been treated in these ways.

Clinical Effects of Tumours

- Local effects due to compression, invasion, ulceration or destruction of adjacent structures
- Metabolic effects due to appropriate or unexpected neoplastic cell products
- Effects due to metastases if tumour is malignant.

The clinical effects of tumours are attributable to their location, their cell of origin and their behaviour.

Local Effects

Tumours exert local effects through compression and displacement of adjacent tissues and, if malignant, through their destruction by actual invasion. These effects can be clinically inconsequential if the organ is large relative to the size of the tumour or if no vital structure is threatened. However, even benign tumours can have life-threatening effects on neighbouring structures; for example, a functionally inactive adenoma of the pituitary gland may obliterate the adjacent functioning pituitary tissue, such is the confined space in which the gland sits, resulting in hypopituitarism.

Malignant tumours obviously have more serious local effects because they invade and destroy local structures. This may be fatal if a vital structure is eroded, for example a pulmonary artery by a carcinoma of the lung. In the case of basal cell carcinoma of the skin ('rodent ulcer'), its local effects are sufficient to justify the label 'carcinoma' because, although the tumour rarely metastasises, its invasiveness can be very disfiguring.

Malignant tumours on mucosal surfaces are often ulcerated. Blood can ooze from these lesions; this blood loss can be occult in the case of gastrointestinal tumours and this is a very important cause of anaemia. Ulcerated surfaces also expose the patient to the risk of infection.

Metabolic Effects

Tumour-Type Specific Effects

Well-differentiated tumours often retain the functional properties of the parent tissue. Since such tumours are relatively autonomous and because the total number of functioning cells often greatly exceeds that in the normal organ, clinical effects are common. For example, in the case of endocrine tumours:

- thyrotoxicosis may result from a thyroid adenoma

- Cushing's syndrome may result from an adrenocortical adenoma

- hyperparathyroidism may result from a parathyroid adenoma.

Sometimes the metabolic consequences of a tumour are unexpected or inappropriate, at least in the light of our current knowledge; for example, oat-cell (small-cell) carcinomas of the lung commonly secrete ACTH and ADH, although this rarely gives rise to clinically significant consequences.

Other specific tumour-associated phenomena have no metabolic consequences but are nevertheless probably mediated by humoral facttos. The most common example is finger-clubbing and hypertrophic osteo-arthropathy in patients with carcinoma of the lung.

Non-Specific Metabolic Effects

The catabolical clinical state of a cancer patient with severe weight loss and debility is known as *cachexia* and it thought to be mediated by tumour-derived humoral factors that interfere with protein metabolism. Cachexia can also occur wuitte early in the course of the disease, notably in patients with carcinoma of the lung. Weight loss can, of course, also be due to interference with nutrition because of, for example, oesophageal obstruction, severe pain or depressive illness.

Neuropathies and myopathies are associated with the presence of malignant neoplasms, particularly with carcinoma of the lung. A tendency to venous thrombosis is associated with mucus-producing adenocarcinomas, notably of pancreas. Glomerular injury can result from deposition of immune complexes in which one of the ingredients is tumour antigen.

Tumour Dormancy

After surgical removal, radiotherapy and/or chemotherapy there may be no clinically detectable tumour remaining in a patient. Occult tumour foci can remain clinically dormant for perhaps several years before their regrowth causes signs and symptoms. For this reason, it is virtually impossible to speak of a cancer patient as being 'cured', and prognosis can be given only in terms of the probability of survival or the length of the disease-free interval.

Prognosis and Its Prediction

Malignant tumours have a variable prognosis. This is determined partly by the innate characteristics of the tumour cells (i.e., growth rate, invasiveness), and partly by the effectiveness of modern cancer therapy for individual types of tumour.

The patient's treatment is guided by the most accurate determination of:

- tumour type (i.e., melanoma, squamous cells carcinoma, leiomyosarcoma)

- grade or degree of differentiation

- stage or extent of spread

- stromal features such as lymphocytic infiltration.

Tumour Type

The tumour type is usually determined from the growth pattern of the tumour and its relationship to the surrounding structures from which an origin may be evident. Thus, a gland-forming neoplasm in the breast is most likely to be a primary adenocarcinoma of the breast, particularly if carcinoma cells are also present within the original breast ducts near the tumour (intraduct carcinoma). A squamous cell carcinoma is often recongisable from the production of keratin, and it may be in continuity with adjacent squamous epithelium, possibly showing carcinoma in situ.

Tumour Grade

The grade of a tumour is an assessment of its degree of malignancy or aggressiveness. This can be inferred from its histology. The most important feattures contributiong to the assessment of tumour grade are:

- mitotic activity

- nuclear size and pleomorphism

- degree of resemblance to the normal tissue (i.e., differentiation).

Tumours are often heterogenous, and the grading should be performed on what appears to be the least differentiated area as this is likely to contain the mostt aggressive clone or clones of tumour cells.

Tumour Stage

The stage of a tumour is the extent of spread. This is determined by histopathological examination of the resected tumour and by clinical assessment of the patient, often involving imaging techniques. Perhaps the best known staging system is that devised by Cuthbert Dukes for colorectal carcinomas:

- Dukes' A: invasion into but not through the bowel wall

- Dukes' B: invasion through the bowel wall but without lymph node metastases

- Dukes' C: involvement of the local lymph nodes

Dukes' D (a stage added by some surgeons): hepatic metastases present.

The most generally applicable staging system is tthe TNM system:

- 'T' refers to the primary tumour and is suffixed by a number that denotes tumour size or local anatomical extent. The number varies according to the organ harbouring the tumour.

- 'N' refers to lymph node status and is suffixed by a number denoting the number of lymph nodes or groups of lymph nodes containing metastases.

- 'M' refers to the anatomical extent of distant metastases.

Stromal Features

Many surveys have shown that tumours showing infiltration of their stroma by lymphocytes and other defensive or immune cells have a better prognosis than tumours lacking such infiltrates.

Early Detection of Cancer

The success of early diagnosis relies upon finding tumours at a curable stage before they have had a chance to spread from their site of origin. This is best achieved by screening asymptomatic people, concentrating on those at greatest risk, in the hope of detecting very early lesions.

Cervical intra-epithelial neoplasia (CIN) can be detected by exfoliative cytology of the cervix. Cells are scraped from the cervix, smeared on to glass slides, stained, and then examined by a cytologist trained to detect abnormalities.

Breast cancer can be detected at an early stage by regular screening by mammography, followed by diagnosis by fine needle aspiration cytology or biopsy.