Cancer holds a strange place in modern mythology.

**Incidence**

It is a common disease.... 1 person in 3 can expect to contract some form of cancer at some stage in their lifetime, and 1 person in 5 can expect to die from it (means 4 out of 5 won't die from it -
heart disease is a much more common cause of death, but doesn't seem
to carry the gloomy overtones of a diagnosis of cancer. There is also a
line of thought that says given what we know about the inherent
instability and innate chemical reactivity of DNA, and that it is now quite
clear that cancer is a disease which results from mutations in the DNA,
the surprise is that cancer is not more common than it actually is.)
Worldwide, 100 to 350 of every 100,000 will die of cancer each year.
Given the global population of about $6.4 \times 10^9$ this implies 6.4 to 22.4
million people will die of cancer this year- roughly between 17000 to
61000 per day, or 730 to 2500 during the time it takes to give this lecture.
It is clearly something we would like to know more about and would like
to control.
Although cancer has been known since human societies began recording their activities (it was well known to the ancient Egyptians and to succeeding civilisations) it has only attained prominence in more recent times. This is because most cancers (as we shall see) manifest themselves late on in life, so that until the expectation of life began to increase significantly -from the middle of the 19th century onwards,- the number of people surviving into the 'cancer age' was relatively small.

( Note that the data above is plotted on a log scale)

Increased health care and advances in medicine means that the major infectious diseases and diseases of childhood that were the major causes of death in the past are now much more controlled, and cancer is now a major problem for our ageing population.

Note however that although most cancers appear late in life the incidence of some cancers peaks at a particular age and later become less prevalent. Some cancers show peak incidence early in life.
Retinoblastoma (cancer of the eye) and Wilms tumour (a nephroblastoma, a cancer of the kidney) are predominantly childhood cancers and are associated with inherited gene defects (Rb in the case of retinoblastoma and WT1 and/or WTX in Wilms tumour). Testicular cancer peaks at age 35, thyroid cancer at age 60 and breast cancer at age 80.

**Some basic tumour biology.**

As a start point to help understand what happens in the development of tumours and cancers it is worth considering normal tissue structure.

Each tissue has its own specific cells, usually several types, which make up the tissue structure. However, this tissue structure follows a fairly standard and consistent pattern (outlined below see Fig 1.1 in Franks and Teich)

---

![Typical Tissue Structure](image)


A layer of epithelium (the tissue specific cells) is separated from the supporting mesenchyme by a basement membrane. The support tissue
(or stroma) is made up of connective tissue and fibroblasts and may be supported on a layer of muscle or bone depending on the organ. In some tissue such as the skin or intestine the epithelium maybe several cells thick. It may form tubes as in the kidney or lungs, or solid cords as in the liver, but the basic pattern remains the same. Different organs vary in the nature of the specific cells and in the arrangement and distribution of the supporting mesenchyme, but the basic pattern is maintained.

During normal development and throughout adult life proliferation and cell death are carefully regulated to ensure proper growth to adulthood and the maintenance of the adult state. Cell birth and death rates determine adult body size. Some adult tissues show constant and continuous cell proliferation as constant tissue renewal strategy. Intestinal epithelial cells for example have a life time of just a few days before they die and are replaced. Some of the white blood cells are replaced as rapidly and skin cells live for about 2 to 4 weeks before being shed. The cells of many adult tissues however do not normally divide except during healing processes.

Tumour cells and cancer cells however divide inappropriately. Before considering this further it is worth just highlighting the different stages of cancer development and reminding you of, or acquainting you with, some of the terminology associated with the cancer field. Fig 1.2 from Franks and Teich
And Fig 23-7 from Lodish.(below)

Particularly worth noting from this figure is the fact that colon cancer is the result of multiple gene mutations. It is now generally accepted that between 5 and 8 genes need to be mutated before a malignant tumour is produced. This is believed to hold for all tumours, not just the colon tumours illustrated here. Each mutation creates a cell increasingly well adapted for autonomous growth. However, since the probability of a single cell simultaneously acquiring these mutations is vanishingly small, this sequential process of acquisition of mutations can only be achieved if cells bearing the initial mutation, the so-called initiated cells, clonally expand until the population increases to many millions. A second mutation at a critical locus in one of these cells then occurs which gives this cell a growth advantage and a second clonal expansion of this cell...
bearing 2 mutations occurs. The repeated process of clonal expansion allows subsequent mutations to be amassed and cells become progressively better adapted to an independent life until a full blown malignant cell finally results.

Do cancers arise from a cancer stem cell?
The traditional view of cancer development is outlined in part 'a' of the figure below. The cells of the tumour are considered to be heterogeneous, but most, if not all, can grow readily and give rise to new cancer tissue. A more recent concept which has developed over the last decade is shown in part 'b' which illustrates the 'cancer stem cell' theory. Here the cancer cells are heterogeneous (as in 'a') but only the stem cells, which typically are only 1 to 2% of the total tumour, can proliferate extensively and give rise to new tumours. These cells, like the stem cells in normal tissues, can both self renew and produce differentiated daughter cells.

There is increasing support for the 'cancer stem cell' view of tumour growth, but whether all tumours arise from a stem cell isn't certain. Nor is it clear yet if the cancer stem cell arises from malignant changes in a
normal stem cell, or whether a differentiated cell within the tissue undergoes some degree of de-differentiation and adopts a 'stem cell like' phenotype, though currently the former view is considered more likely. The notion that there is a stem cell population which sustains the tumour growth has started to modify thoughts of how cancer therapy should be approached.

**Tumours generally classified into 3 main groups**

1). **Benign tumours.**

<table>
<thead>
<tr>
<th>TUMOUR CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENIGN TUMOURS</td>
</tr>
<tr>
<td>Develop in any tissue</td>
</tr>
<tr>
<td>• grow locally</td>
</tr>
<tr>
<td>• May cause problems by pressure (brain) or obstruction (colon)</td>
</tr>
<tr>
<td>• Histologically resemble the tissue of origin</td>
</tr>
<tr>
<td>• Covering or lining tissues of skin, intestine, bladder etc may produce wart-like outgrowths containing all cell types</td>
</tr>
<tr>
<td>• In other situations only one cell type may be present- may produce an excess of particular hormone</td>
</tr>
<tr>
<td>• Benign does not mean 'completely harmless'</td>
</tr>
<tr>
<td>• Do not spread to distant sites</td>
</tr>
</tbody>
</table>

These may develop in any tissue, grow locally and may cause problems by local pressure (brain tumours, usually of the support tissue, not the nerve cells themselves, cause damage because of the physical constraints of the skull) or obstruction (as in the colon. It is worth mentioning that tumours of the small intestine are relative rare,
despite the high rate of cell turnover in the villus. High proliferative rates are not necessarily linked to a high incidence of tumour formation). Histologically, the benign tumours resemble the tissue of origin. ie. Cytologically, the specific tumour cells do not differ substantially in structure from the cells of the tissue of origin. Benign tumours of cartilage or bone may produce nodules indistinguishable histologically from normal tissue. The covering or lining tissues of the skin, intestine, bladder etc may produce wart-like outgrowths which contain all the cell types closely packed to form a solid nodule. In other situations only one cell type might be present, and in this case these tumours might produce an excess of a particular hormone produced by that cell type, so benign doesn’t necessarily mean completely harmless. The common feature is that they do not spread to distant sites.

2). In situ tumours.

<table>
<thead>
<tr>
<th>TUMOUR CLASSIFICATION \nIN SITU TUMOURS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually develop in the epithelium</td>
</tr>
<tr>
<td>Usually small</td>
</tr>
<tr>
<td>• Have altered histological appearance</td>
</tr>
<tr>
<td>• Loss of normal arrangement of cells</td>
</tr>
<tr>
<td>• Variations in cell size and shape, increase in nucleus size and staining (increased DNA), presence of abnormal chromosomes</td>
</tr>
<tr>
<td>• Do not invade basement membrane and supporting mesenchyme</td>
</tr>
</tbody>
</table>
Usually develop in the epithelium and are usually small. The cells have altered histological appearance and show morphological characteristics of tumour cells to a greater or lesser degree. Such changes include loss of any normal regular arrangement of the cells, variations in cell size and shape, increase in nuclear size and staining (reflecting increased DNA content), increase in mitotic activity, the presence of abnormal chromosomes. They do not invade the basement membrane and supporting mesenchyme.

3). Cancers.

<table>
<thead>
<tr>
<th>TUMOUR CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANCERS</td>
</tr>
</tbody>
</table>

- Fully developed malignant tumours with the specific capacity to invade and destroy the underlying mesenchyme.
  - Metastasise
  - Stimulate angiogenesis and development of blood supply
  - In contrast to primary tumours which have not invaded the underlying tissue and metastasised and which may be treated by surgery, or localised radiotherapy or chemotherapy, tumours which have metastasised are much more difficult to treat.

Fully developed malignant tumours with the specific capacity to invade and destroy the underlying mesenchyme. The tumour passes through the basement membrane and invades the underlying tissues and then invades the blood vessels allowing individual tumour cells, or small clumps of tumour cells, to escape from the original, primary tumour, and make their way around the body via the blood stream. These cells may
then escape from the blood stream and invade other organs giving rise to secondary tumours. This process is known as metastasis. Like normal tissues, tumour cells need nutrients that are normally provided to normal tissues by the blood stream and some tumours will produce agents which stimulate the growth of new blood vessels into the tumour. The new blood vessels are easily damaged and may increase the possibility for the tumour to metastasise and produce secondary tumours elsewhere. Primary tumours which have not invaded the underlying tissues and have not metastasised are often treatable by surgery or by localised chemotherapy or radiotherapy, and there is a good chance of the patient surviving. Tumours which have metastasised are much more difficult to treat.

Overview of tumour formation.
Cancer formation is the conversion of normal cells, which respond to homeostatic feedback mechanisms which regulate cell proliferation, to cells capable of autonomous growth and invasion- the cancer cells.
Cancer arises as a result of alterations to the DNA. ie as a result of gene mutation. The majority of such mutations occur in the somatic cells (which includes the stem cell populations in a particular tissue) rather than the germ line cells (eggs and sperm) and are not usually passed onto the next generation. There are however a small number of germ-line mutations which are passed onto the next generation and which increase the probability of cancer developing.

The human body contains of the order of $10^{15}$ cells, many of which normally will continue to divide and differentiate even in the adult human. Obvious examples are the cells in the basal layers of the skin
which divide, differentiate and are finally sloughed off, and cells in the
epithelial layer of the intestines which are replaced roughly every 10
days, and cells in the bone marrow which produce white cells which may
last for as little as 24h.

Even tissues such as adult liver, which show very low rates of division
under normal conditions, can show high rates of proliferation following
trauma or infection.

It has been estimated that there are about $10^{11}$ or $10^{12}$ cell divisions per
day.

The mutation rate has been estimated at about 1 per $10^6$ genes, per cell
generation, which means that millions of cells carrying random
mutations are generated every day. At first sight this might be expected
to generate many more tumours than are actually observed, but the
multistep theory of tumour development requires that multiple
independent mutations must occur within a single cell. The likely hood
of this happening clearly increases with age.

Genes that alter the rate of cell formation or the rate of cell death (which
are exquisitely balanced in the normal adult tissue) are the genes which
allow cells to escape from the usual homeostatic mechanisms. The
altered cellular regulatory processes which are most likely to be
modified by mutations and which eventually lead to cancer are shown in
Fig below.

Six different fundamental cellular properties may be altered to give rise to the complete, most aggressive and destructive cancer phenotype. Less dangerous tumours arise when only some of these changes occur. (The ability to invade and metastasise defines the most aggressive types, but benign and in-situ tumours will have some level of manifestation of the other changes).

Hanahan and Weinberg suggest that the vast range of cancer cell genotypes result from alterations in six essential features of cell physiology, and that collectively these changes define the extent or degree of malignant growth (See Figure.):

The six altered processes defining the malignant state are:

- self-sufficiency in growth signals,
- insensitivity to growth-inhibitory (antigrowth) signals,
- evasion of programmed cell death (apoptosis),
- limitless replicative potential,
• sustained angiogenesis,
• tissue invasion and metastasis.

Each of these physiological changes—novel capabilities acquired during tumor development—represents the successful breaching of an anticancer defence mechanism hardwired into normal cells and tissues. They suggest these six capabilities are shared in common by most and perhaps all types of human tumors. This multiplicity of defenses may explain why cancer is relatively rare during an average human lifetime. The extent to which each novel capability is manifest probably varies from tumour to tumour.

The figure from Lodish (below) of gross morphology of metastatic lung tumour growing in human liver certainly suggests wide differences in the degree of sustained angiogenesis. Some of the tumours are clearly very white and probably lacking in blood supply (as are many secondary liver metastases from primary colon cancers) whilst others appear much redder and appear to have a much better blood supply.
End Lecture 1