Lecture Notes on Clinical Oncology

Barry W Hancock
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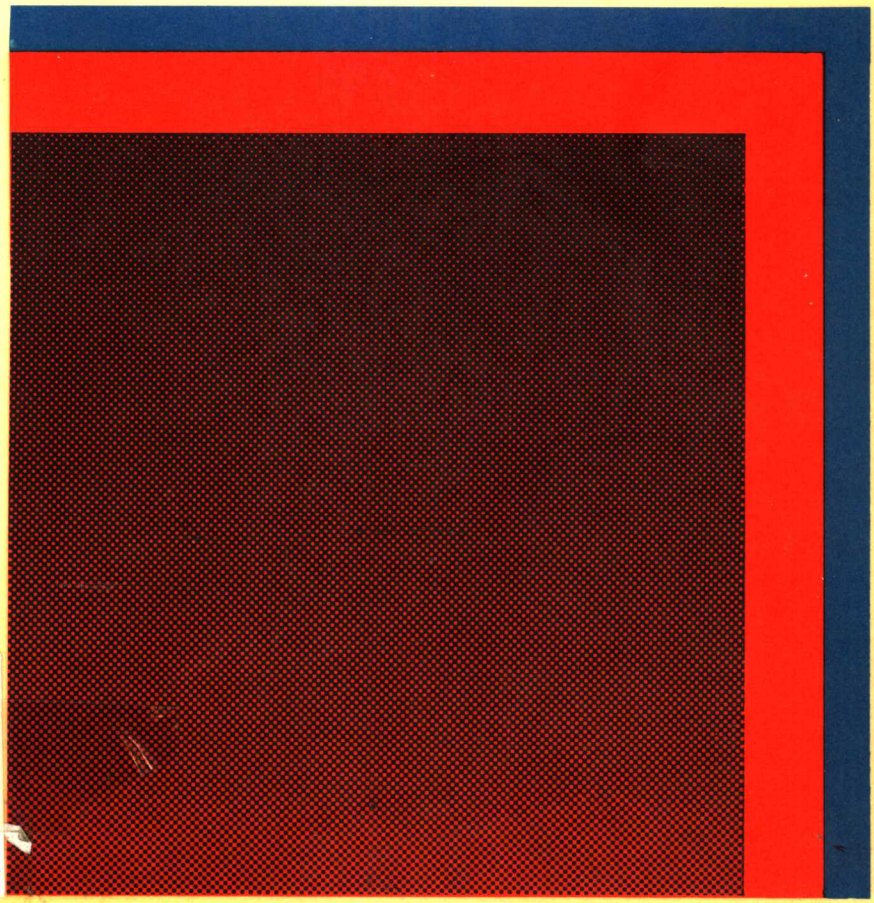

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LECTURE NOTES ON

Clinical Oncology

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Preface

This new book in the 'Lecture Notes' series is aimed at senior undergraduate students and recently qualified practitioners in all specialities; it is intended as an up-to-date guide to the theory and practice of all aspects of clinical oncology and should provide insight into the diverse nature of the subject, emphasising the multidisciplinary approach necessary for the successful management of the patient with cancer. We hope that our attempt to cover such a large field concisely will not contain too many omissions or dogmatisms. We are grateful to Professor J. Richmond, Dr. F. E. Neal and Dr. E. M. Pickering for helpful criticism and to the Department of Medical Illustration, Royal Hallamshire Hospital, Sheffield, for their help with many of the figures.

Barry W. Hancock
J. David Bradshaw

Contents

Chapter 1
Cancer Overview

INCIDENCE AND EPIDEMIOLOGY

Impressions can be very misleading, and this is especially true in respect of the incidence of malignant disease. A worker in general practice might well regard the overall incidence as low; one in a general hospital is likely to regard it as higher; one in a specialist oncological hospital might get the impression that it is very common.

In fact, in the United Kingdom about three new cases are diagnosed each year for every 1000 of the population. One in every five persons born is likely to develop some form of the disease at some time during life. The average general practitioner will see seven new cases each year, but will see some types of malignancy very rarely. Cancer is not the commonest cause of death; the annual death rate from cardiac diseases is approximately three times that from malignant disease.

Cancer registration

With the development of cancer registration schemes, accurate estimations of the incidence of the disease in general and of its different types have become possible. It has become evident that overall the incidence has changed little over the past 50 years.

The registration of new cases on presentation provides a much more accurate estimation of incidence than do mortality statistics. Successfully treated malignant disease may not contribute to an individual's death, and therefore may not feature in the certified cause of death. Nevertheless, the incidence of death from the disease must rank high in the emotional reactions to the disease of people in general.

Changing incidence of diseases

Since the beginning of the present century, there has been a steady reduction in the infant mortality rate, due in large part to improved neonatal care, and more recently to the availability of antibiotics.

Whereas the principal causes of death in early life were infectious diseases, tuberculosis and other lung diseases, malignant disease now shows a relatively increased incidence in childhood.

Age and sex incidence of malignancy

The incidence of malignancy increases with age for most types of the disease. However, it is higher in the first five years of life than in the next two 5-year periods, due principally to leukaemia, to tumours of the central nervous system and to embryonal tumours.

In an increasing and ageing population the number of patients developing the disease will increase, even though the incidence at any age remains the same, and despite the fact that the chance of dying of the disease at any one age gradually is decreasing.

The overall incidence is the same in males and in females, but the relative rates vary with age. Below the age of ten years, it is higher in males than in females; over the period 20–60 years it is somewhat higher in females, especially in the period 35–50 years due to the relatively high incidence of malignancy of the breast and uterine cervix; over the age of 60 years, the incidence in males is markedly higher than that in females. Fig. 1.1 reflects approximately the overall incidence of the disease by age.

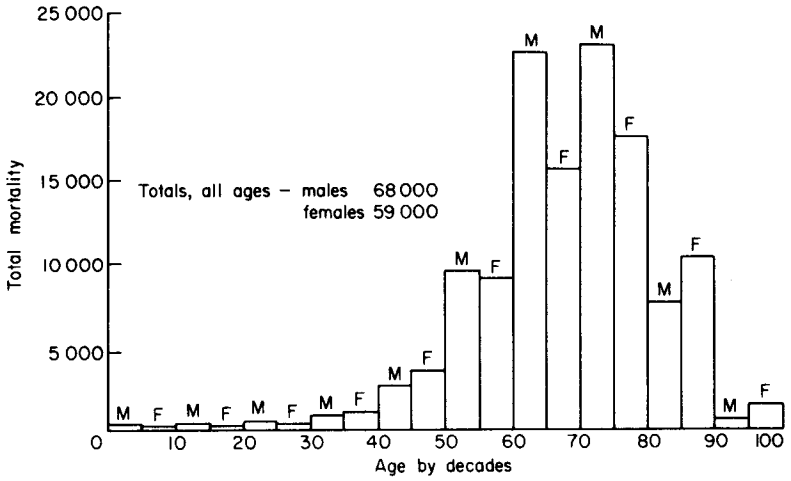

Fig. 1.1. Malignant disease; overall mortality by decades, England and Wales 1976. (Based on Government Statistical Service data from *Mortality Statistics—Cause.*)

In western countries, the order of overall incidence of malignant diesase for each sex and site is shown approximately in Table 1.1 and Fig. 1.2.

Table 1.1. Incidence by site.

Males (%)	Females (%)
Bronchus (30)	Breast (25)
Digestive tract (20)	Digestive tract (20)
Urinary tract and prostate (15)	Uterus (10)
Skin (10)	Skin (10)
	Bronchus (5)

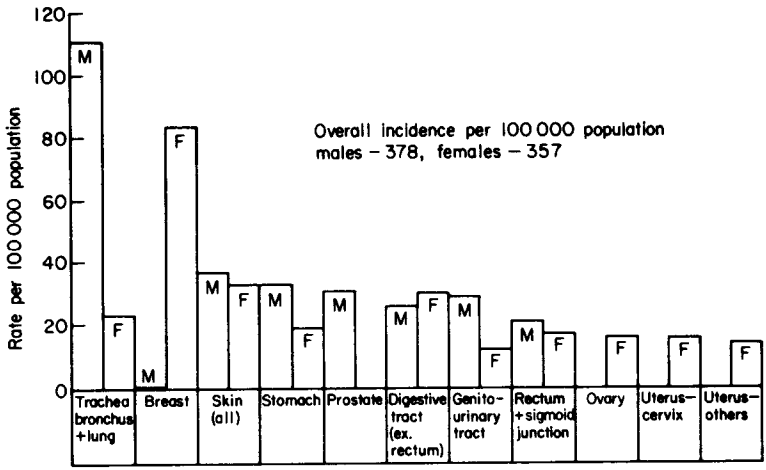

Fig. 1.2. Incidence of malignant disease by site. (Based on Trent Regional Health Authority data from *Radiotherapy Statistical Tables for 1977.*)

The predominating type of malignancy also varies with age. In children of both sexes up to the age of ten years, brain tumours and the leukaemias are commonest. In males, testicular tumours are commonest in the age range 20–30 years, carcinoma of the bronchus is commonest in the age range 45–65 years, and adenocarcinoma of the prostate is commonest over the age of 70 years. In females, carcinomas of the breast and

uterine cervix are commonest in the age range 25–65 years, and the predominance of carcinoma of the breast persists at all ages thereafter.

Geographical factors in incidence

The incidence of malignant disease can show marked variations between different countries and between different races. An outstanding example is the very low incidence of carcinoma of the uterine cervix in Jewish women. Other examples include the very high incidence of carcinoma of the postnasal space in the Chinese, the high incidence of malignancy of the uterus in Indian women, of primary liver malignancy in South and West Africans, of bladder malignancy in Egyptians, of stomach tumours in Japanese and Scandinavians, and the very low incidence of breast malignancy in the Japanese.

It is of great interest, however, to note that, in general, immigrant populations tend to assume the pattern of incidence appropriate to their adopted country, suggesting that environmental factors have a major role in aetiology.

Table 1.2. Standardised mortality ratios by occupation, England and Wales 1970–72. (Based on Government Statistical Service data from *Social Trends*.)

Site	Professional and other		Intermediate		Skilled				Partly skilled		Unskilled	
					Non-manual		Manual					
	M	F	M	F	M	F	M	F	M	F	M	F
Trachea, bronchus and lung	53	73	68	82	84	89	118	118	123	125	143	134
Uterine cervix	–	<20	–	66	–	69	–	120	–	140	–	161
Breast	–	117	–	121	–	110	–	109	–	103	–	92
Prostate	91	–	89	–	99	–	115	–	106	–	115	–

Social factors in incidence (Table 1.2)

These environmental factors may be related to local geographical conditions, or to different life styles and habits. In females the age of marriage, the number of pregnancies and the attitude to breast feeding may be relevant. To some extent, these factors may be determined by the degree of economic development of the country, and the associated social and economic status of the population. It is becoming increasingly evident that environmental factors are responsible for many forms of malignant disease.

Industrial factors in incidence

As will be seen in more detail later the increased risk of workers in some industries developing malignant disease is well recognised. As long ago as 1775, Percival Pott noted an association between carcinoma of the scrotal skin and chimney sweeping as an occupation. Earlier this century, the tendency to develop similar tumours in mule-spinners became evident, this being related to the period when certain mineral oils were used to lubricate the spindles of the mules.

More recently, an increased incidence of bladder carcinomas in workers in the azo-dye industry and in the rubber and cable industries has been recognised. Workers having prolonged contact with tar and pitch show a tendency to develop warty lesions in the exposed skin, and these can progress to become carcinomas. Prolonged contact with arsenical compounds can have similar effects.

Inhalation of dust containing chromates or dichromates can lead to lung malignancy; even more active is asbestos dust, which can result in tumours of the pleura (mesotheliomas) as well as of the bronchial mucosa. Long-term inhalation of benzol vapour can result in bone marrow changes ranging from anaemia and pancytopenia to leukaemia.

Prolonged exposure of the skin to strong sunlight will result in a higher than average incidence of keratotic lesions which have a marked tendency to undergo malignant change. This is seen, for example, in Indian tea planters and in Australian sheep farmers.

Exposure over long periods to ionising radiations also can induce skin malignancies; this was seen particularly in early radiation workers, some of whom accumulated relatively large doses to the hands before the dangers were recognised.

All these forms of malignant disease are related to identifiable chemical carcinogens or to physical agents which can have carcinogenic effects. Once recognised, steps can be taken to limit or prevent exposure, or to introduce alternative non-carcinogenic agents in industry.

Mortality from malignancy

For many forms of the disease, mortality rates are showing a gradual fall; this is true particularly for malignancy of the stomach, uterus, bones and tongue. Malignancy of the pharynx is showing a fall in females but not in males. A rise in mortality is evident for malignancy of the ovary, pancreas, bladder, kidney and lung, and for the leukaemias and the lymphomas. The increasing mortality from carcinoma of the lung (bronchus) is most striking.

The overall mortality for males is higher than that for females. This is

due to the higher incidence of malignancies of lower curability in males, especially bronchial and gastric carcinomas.

Changing mortality patterns therefore reflect firstly the changes in incidence and detection and secondly the effects of therapy on different tumours.

AETIOLOGY

The precise cause of cancers is still unknown but it is likely that many, if not all, have a multifactorial aetiology. Genetic and environmental factors are important (Table 1.3).

Table 1.3. Factors related to the cause of cancer.

GENETIC
Familial predisposition to cancer
Chromosomal abnormality associated with increased incidence of cancer
Inherited syndromes associated with increased incidence of cancer
Histocompatibility antigen status predisposing to cancer
ENVIRONMENTAL
Irradiation
Chemicals
Viruses
Hormonal
Immunological
Chronic irritation

Genetic factors

There is evidence that individuals with certain genetic make-ups are more susceptible to cancer though there is rarely a predictable mode of inheritance.

FAMILIAL PREDISPOSITION

Some tumours occurring in children have a strong hereditary predisposition. One form of childhood retinoblastoma appears to be inherited as a dominant trait. Nephroblastoma, neuroblastoma, phaeocromocytoma and neurofibromatosis also have a strong familial element.

CHROMOSOMAL ABNORMALITY SYNDROMES

In certain types of chromosomal abnormality disorders the incidence of

neoplasia is increased. In Down's syndrome (trisomy 21) acute leukaemia is a well-known complication. This complication is also found in Klinefelter's syndrome (XXY) a condition in which breast carcinoma is also more common.

ASSOCIATED INHERITED SYNDROMES

Certain immunodeficiency syndromes are associated with an increased incidence of cancer. Ten per cent of patients with ataxia telangiectasia (an autosomal recessive disorder with telangiectasia, progressive ataxia and variable mixed immunodeficiency) and Wiskott-Aldrich syndrome (X-linked recessive immunodeficiency with eczema and thrombocytopenia) die of malignant diesase, and the incidence may well be higher in patients with other variable immunodeficiency states. Lymphoreticular malignancy seems to be the commonest complication but the incidence of epithelial malignancy is also unexpectedly high.

Other 'non-immunodeficiency' disorders seem to predispose to cancer. Xeroderma pigmentosum, a skin condition with enhanced sun light sensitivity and increased incidence of skin and subcutaneous cancers, and polyposis coli predisposing to colonic carcinoma, are examples of these.

HISTOCOMPATIBILITY ANTIGEN STATUS

The histocompatibility antigen (human leucocyte antigen, HLA) system is a genetically determined single major transplantation antigen system which plays an important part in determining susceptibility and resistance to disease. Particular HLA types are associated with malignancy, for example with Hodgkin's disease (A1, B5, B8) breast carcinoma (A10, B18) and acute lymphatic leukaemia (A2).

An apparent increase of common cancers is often seen in family groups; these could arise from some shared genetic characteristic, possibly HLA-mediated susceptibility, or equally from the action of similar environmental factors in a close-contact group or indeed from a combination of both.

Environmental factors

IRRADIATION

Ionising irradiations have the capacity to displace electrons from atoms

thus converting them to ions. They can therefore cause chemical changes within living cell molecules the most important being the damage to the susceptible nuclear DNA with consequent changes in the structure and linkage of spiral strands. If these changes are severe enough cell death will result; less severe changes may cause the cells to become permanently altered in such a way as to escape normal control mechanisms—i.e. to become neoplastic.

Several examples of radiation induced tumours can be found. The high incidence of skin cancers in early x-ray workers, of lung cancer in the miners of radioactive ores, of bone tumours in girls who painted luminous watch dials (with radioactive radium), of thyroid cancer in people who survived the atomic bomb blasts or who had neck irradiation in childhood for some reason, and of leukaemia in patients with ankylosing spondylitis treated by radiotherapy, all suggest that radiation induces mutations in the genetic material of cells in the irradiated tissues.

Sunlight, by virtue of its ultraviolet irradiation, may over the years cause skin cancer in fair skinned people, presumably by damaging DNA in skin cells.

Table 1.4. Chemical carcinogens and cancer.

OCCUPATIONAL EXPOSURE	
Asbestos (lung)	
Arsenic (skin, lung)	
Chromium (lung)	
Nickel (lung, paranasal sinuses)	
PVC (liver)	
Organic chemicals (lung, skin, bladder)	
—petroleum fractions	
—aromatic amines	
—benzene	
ENVIRONMENTAL AND FOOD	
Aromatic hydrocarbons, Asbestos	atmospheric (? lung)
Arsenic—drinking water	(skin)
Aflatoxin—moulds	(liver)
Preservatives (?)	
SOCIAL CUSTOMS	
Tobacco smoking	(lung, oesophagus)
IATROGENIC	
Arsenic	(skin)
Cytotoxic drugs	(various)
Immunosuppressive drugs	(various)
Exogenous hormones	(various)

CHEMICALS

A list of the better known of the chemical carcinogens is given in Table 1.4. Many of them (probably more than 10%) are encountered during occupational exposure. Chemical carcinogens may be active in their primary form (direct acting) or may need to be modified in the body before becoming active (procarcinogens). Interference with nuclear DNA is again the main mechanism of oncogenesis.

Occupational. The most important occupational carcinogens are asbestos, arsenic, benzene, chromium, nickel and petroleum fractions and it is important to remember that exposure to several of these chemicals can occur in one man's working lifetime with possible carcinogenesis of a number of tumours (e.g. lung carcinoma, mesothelioma, head and neck cancers). As has been seen, historically the soot induced scrotal carcinoma of chimney sweeps and the aniline dye induced bladder cancers achieved notoriety. More recently the effects of asbestos, particularly on the lung, of industrial mineral oils on the skin and of polyvinyl choloride (PVC) on the liver have provided the main debating points on chemical carcinogenesis.

Environmental. The importance of urban atmospheric pollution (e.g. with aromatic hydrocarbons and asbestos particles) in carcinogenesis is still uncertain. The places of arsenic in drinking water of certain populations as a cause of skin cancer and of aflatoxins from *Aspergillus flavis* in the staple foodstuffs of certain tropical peasants as a cause of liver cancer seems undeniable.

There are undoubtedly substances, (e.g. nitrosamine), used as preservatives or colouring reagents in everyday foods, which if present in large enough quantities could be carcinogenic. The amounts present in food however are minute and the hazards which they present are uncertain.

Social customs. Indisputably the main offender in this category is the habit of cigarette smoking—the carcinogenic effects of which are well known.

Iatrogenic. Iatrogenic (doctor induced) chemical carcinogenesis is of uncertain importance but the effects of our new medications on the population may take years to evaluate. The carcinogenic problems seen at the present times are mainly related to the use of immunosuppressive and cytotoxic drugs in cancer, transplantation and autoimmune disease and to the use of exogenous hormones (e.g. anabolic steroids and liver cancer, prenatal oestrogens and vaginal carcinoma).

VIRUSES

Several types of virus have been implicated in various animal tumours, both naturally occurring and experimentally induced. Perhaps the most important are the Polyoma and SV40 (Papova) viruses, which have been very useful in experimental cancer research and the herpes type viruses, which have been incriminated in Marek's disease—a lymphoproliferative disorder of chickens.

There is no conclusive evidence of viral oncogenesis in man but circumstantial evidence suggests that infection may be an important cause in certain tumours. The occurrence of time-space clusters of patients with Hodgkin's disease and leukaemia is very suggestive of an infective aetiology. In carcinoma of the cervix an aetiological association with herpesvirus is now apparent. In both these conditions however, other environmental factors may be equally important.

No discussion of viral oncogenesis would be complete without mention of Burkitt's lymphoma. Patients with this type of lymphoma occur in clusters, invariably have antibodies to the Epstein-Barr virus and the virus has been isolated from cultured Burkitt's lymphoma cell lines. However the virus does in fact also cause infectious mononucleosis, a benign self-limiting infection, and it is difficult to see how the same virus could cause two such different disorders without some major host-virus adaptations. It now seems likely that chronic severe malaria depresses the host immunity in such a way as to allow continued infection with the virus and subsequent oncogenesis.

HORMONAL

Perhaps the most striking example of hormonal influence in cancer is in breast carcinoma. Some breast tumours are hormone responsive and this seems to correlate with the presence or absence of steroid receptor proteins in breast tissue cells. This has considerable therapeutic implications as we shall see later. It is likely that imbalance of endogenous hormones, rather than any direct oncogenic effects of these hormones, predisposes to cancer. Other examples of hormone dependent tumours are prostatic carcinoma and carcinoma of the body of the uterus.

IMMUNOLOGICAL

The role of immunology in the aetiology of tumours will be discussed more fully later. Suffice to say that one theory of oncogenesis is that potentially neoplastic cells are normally eradicated by a competent

immunosurveillance system; should this system become incompetent for any reasons (genetic or environmental) the cells escape control and proliferate thus forming the cancer.

CHRONIC IRRITATION

Cancers can arise at sites of chronic irritation and in relation to scars, foreign bodies and chronic inflammation. Presumably cell damage at these sites gives rise to abnormal tissue differentiation. Oral cancer is probably the best example of this type of carcinogenesis—factors such as pipe smoking, ill-fitting dentures, poor dental hygiene and chronic infection (e.g. syphilis) are all recognised predisposing causes. In carcinoma of the vagina and cervix uteri there is an aetiological association with early coitus and/or poor genital hygiene. Certain chronic diseases also predispose to human cancer. Good examples of this are achlorhydria and pernicious anaemia and stomach cancer, Paterson-Kelly syndrome and post cricoid carcinoma, ulcerative colitis and colonic carcinoma, cirrhosis and hepatoma, Paget's disease and bone sarcoma, bilharzia and bladder cancer.

Summary

In summary the underlying change in cancer is the abnormal differentiation of cells, probably by alteration of nuclear DNA, within the affected tissue. These cells escape normal growth regulating mechanisms and proliferate to form a mass of tissue which grows beyond the normal confines of the tissue of origin. The initiating cause is likely to be multifactorial and many tumours are believed to arise because environmental factors (e.g. virus or chemical carcinogens) are operating in a host whose normal surveillance mechanisms are impaired by genetic predisposition.

TUMOUR BIOLOGY

A tumour is formed when cells from a certain tissue escape the normal growth regulating processes to extend beyond the normal confines of that tissue. The growth (neoplasm) can be benign or malignant. In the latter case the neoplasm has an ability to invade and destroy surrounding normal tissues and to spread to distant sites by a process known as metastasis; malignant tumours are generally termed cancers.

Tumour cells resemble normal cells in that they have the same struc-

tural features. Nuclear information is coded on the double stranded DNA (deoxyribonucleic acid) which is found in the chromosomes. The RNA (ribonucleic acid) is mainly concerned with protein synthesis within the cell cytoplasm. A special type of RNA (messenger RNA) conveys and translates the genetic information from the nucleus to the cytoplasmic RNA. The nucleotides are arranged in a chain-like pattern with sugar and phosphate groups forming alternate links in the chain with nitrogenous bases (cytosine, thymine, adenine and guanine in DNA, cytosine, uracil, adenine and guanine in RNA) attached at each of the sugar units. The DNA complex is composed of two of these spiralling chains linked by hydrogen bonds across the nitrogen base units.

To undergo growth and division, the cell goes through a sequence of changes—the cell cycle.

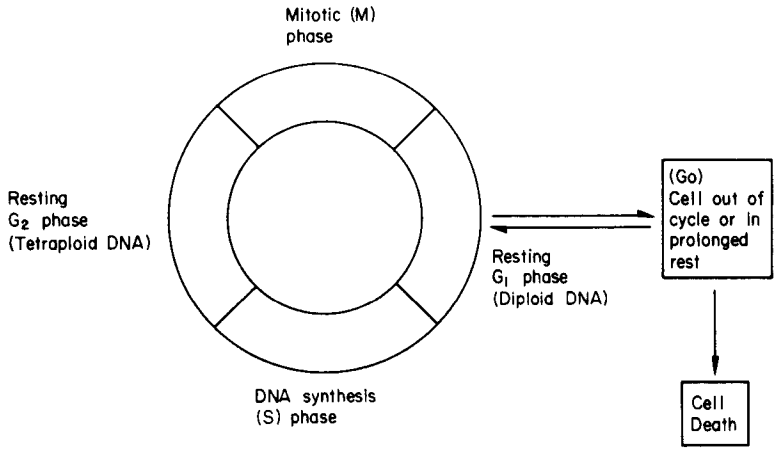

Fig. 1.3. Diagrammatic representation of the cell cycle.

The cell cycle (Fig. 1.3) is an ongoing phenomenon in which cells in cycle are in changeable equilibrium with cells in prolonged rest (G°) phase. Cells in cycle go from an initial resting phase (G1) through a synthetic phase (S) in which the cells DNA content is doubled (tetraploidy) and after a further resting phase (G2) undergo mitosis during which the parent cell splits into two identical daughter cells with identical DNA make-up. After this the daughter cells may recycle or go into prolonged rest (G°).

Most of our information on cell cycling comes from animal and cell