Summary

Clinical cancer chemotherapy in the 20th century has been dominated by the development of genotoxic drugs, initiated by the discovery of the anticancer properties of nitrogen mustard and the folic acid analogue aminopterin in the 1940s. The development of inbred strains of mice in the early part of the 20th century led to the use of transplantable tumors for the screening of very large numbers of compounds, both natural and synthetic, for experimental antitumor activity. Such screening led to the identification of clinically useful drugs at a rate of approximately one every 2 years. New targets for cytotoxicity were identified in this program, including tubulin and DNA topoisomerases I and II. The huge expansion in our basic knowledge of cancer has facilitated the development of two new anticancer strategies: the inhibition of specific cellular growth pathways and the inhibition of growth of cancer as a tissue. One of the most important principles to emerge is that loss of growth control of cancer cells is mechanistically associated with an increased tendency to undergo programmed cell death, or apoptosis. Thus, cancer growth is a balance between cell birth and cell death. The balance is maintained not only by the genetic status of the cancer cell but by interactions with host cells and extracellular matrix components in the tumor environment. The identification of estrogen as a factor for stimulating the growth led to antagonists of growth factor receptor-mediated pathways. The early use of bacterial toxins in cancer treatment has led to strategies based on host–tumor interactions, such as antiangiogenic and immune approaches. Current research has underlined the enormous complexity not only of growth and death control systems within the tumor cell but of interactions of tumor cells with vascular endothelial, immune, and other cells in cancer tissue. The challenge of future development of low-molecular-weight anticancer drugs is to apply knowledge gained in basic studies to develop new strategies.

1. Introduction

It is difficult to assign a date to the beginning of the treatment of cancer with drugs because herbal and other preparations have been used for cancer treatment since antiquity. However, the 1890s, a decade that represents an extraordinarily creative period in painting, music, literature, and technology, encompassed discoveries that were to set the scene for developments in cancer treatment in the 20th century. The discovery of penetrating radiation, or x-rays, by Roentgen in Germany in 1895 was complemented 3 years later by the discovery of radium by Marie and Pierre Curie. The discovery of ionizing radiation led not only to radiotherapy as form of cancer treatment but eventually to the development of anticancer drugs that mimicked the effect of radiation by
damaging DNA. The discovery by George Beatson, working in Scotland in 1896, that the growth of a breast cancer could be halted by removal of the ovaries indicated that the growth of cancer cells in the body could be influenced by external factors. This provided the basis for cancer treatment strategies that changed the regulation of cancer cell growth. The demonstration by William Coley in 1898 that the administration to cancer patients of a bacterial extract, sterilized by passage through a porcelain filter, caused regressions in lymphoma and sarcoma indicated that activation of the body’s defense systems might provide a strategy for cancer treatment. Each of these three advances lent weight to the bold assumption, made by Paul Ehrlich and others in the early part of the 20th century, that low-molecular-weight drugs might be used in the management of cancer as well as infectious diseases. This chapter considers each of these three approaches in turn.

2. Genotoxic (Cytotoxic) Therapy

The first practical anticancer drugs were discovered accidentally. One such discovery was an outcome of war, stemming from the finding that sulfur mustard gas, used as a toxic vesicant in the First World War, caused myelosuppression. Although gas warfare was not employed in the Second World War, a considerable stock of mustard gas canisters was maintained in the Mediterranean area. An accident in the Italian port of Bari, involving leakage of one of these canisters, rekindled interest in the myelosuppressive effect of nitrogen mustard, leading to clinical trials in lymphoma patients (Karnofsky et al., 1948; Kohn, 1996).

The identification of vitamins as small low-molecular-weight enzyme cofactors was an important biochemical achievement in the early part of the 20th century. The structural elucidation and crystallization of folic acid in 1946 led, as with other isolated vitamins, to studies on its effect on the course of a number of diseases. Unexpectedly, administration to leukemia patients of folic acid and its glutamylated derivatives resulted in an increase in tumor growth. While the use of low-folate diets in the management of leukemia was investigated, the development of the folic acid analogue aminopterin provided a significant advance in the management of childhood acute leukemia (Farber et al., 1948; Bertino, 1979).

The link between these two disparate types of drugs and their biological activity was found to be related to their damaging effect on DNA. Although Friedrich Miescher had characterized DNA as a substance in 1862, the informational complexity and significance to life of DNA was not appreciated until the 1940s. The elucidation in 1953 by James Watson and Francis Crick of the double-helical structure of DNA had a singular impact on strategies of anticancer drug development. The cancer chemotherapeutic agent nitrogen mustard was found to react chemically with DNA (Kohn et al., 1966). Studies on aminopterin indicated that it interrupted DNA biosynthesis and in so doing caused DNA damage. The next two decades brought a massive development of new drugs that affected the integrity of the cell’s genetic material, with approximately one new drug entering widespread clinical use every 2 years. Many of these drugs, which revolutionized the treatment of many types of cancer, are shown in Figure 1.

A. Development of in Vivo Cancer Screening Systems

Developments in chromatography and analytical chemistry in the first half of the 20th century allowed compounds of defined structure to be isolated from a variety of plants, animals, and microorganisms (see Chapter 12). The evolution of synthetic organic chemistry over this time provided anticancer drugs in addition to antimicrobial and other medicinal drugs (see Chapter 11). It was quickly realized that it would be impossible to test such a large number of compounds in cancer patients and that some type of model tumor system was required. Transplantable animal cancers became accepted as the best basis for the screening of such drugs. This was made possible by the availability of inbred mouse strains, which had their beginnings in the early part of the 20th century. Three inbred strains of particular importance to anticancer drug screening—DBA, BALB/c, and C57BL—were introduced in 1909, 1916, and 1921, respectively. Spontaneous or carcinogen-induced tumors in these strains could be transplanted from one inbred mouse to another, allowing repeated testing of potential anticancer drugs (Stock, 1954). A detailed description of the role of animal testing in drug development is provided in Chapter 16. In the 1950s and 1960s, most testing programs used the transplantable L1210 and P388 murine leukemia models for primary screening and transplantable solid tumors for more advanced testing (Goldin et al., 1981). The discovery of the athymic “nude” mouse, which had lost its ability to mount a cell-mediated immune response, allowed the testing of new drugs against human tumor material growing as xenografts in such mice (Rygaard and Povlsen, 1969).

B. Mitotic Poisons

Many of the early drugs that were screened for anticancer activity were derived from natural products. The plant product colchicine, isolated from the autumn crocus, was one of the first of these to demonstrate activity against experimental murine tumor models. It was found to induce arrest of cultured cells in mitosis and demonstrated a new mode of induction of genomic damage: that of disturbing the correct distribution of genetic material into daughter cells at mitosis. Colchicine, although useful at lower doses for the treatment
of gout, proved too toxic for use as an anticancer drug, and early attention focused on the Vinca alkaloids from the periwinkle plant (Johnson et al., 1963). Two such alkaloids, vinblastine and vincristine, had a major impact on the early treatment of patients with malignancy (Rowinsky and Donohower, 1991). The protein tubulin was identified as the target for colchicine and the Vinca alkaloids (reviewed by Uppuluri et al., 1993) and is the subject of considerable anticancer drug research. The broadening of the spectrum of tumor types susceptible to spindle poisons resulted from the discovery of the taxane class of compounds. Paclitaxel, discovered as a component of some Taxus species (Wani et al., 1971), escaped detailed investigation until it was found to have a novel biochemical action distinct from that of the Vinca alkaloids, involving promotion rather than inhibition of microtubule assembly (Schiff et al., 1979). Paclitaxel (Rowinsky et al., 1990) and docetaxel (Bissery et al., 1991) have a prominent place in cancer therapy today.

C. DNA-Reactive Drugs

Nitrogen mustard was the basis for the synthesis of a large series of clinically useful derivatives, including melphalan and cyclophosphamide, all found to exert their antitumor effects by alkylation of DNA. Natural products also yielded a number of clinically useful compounds that reacted chemically with DNA, such as mitomycin C (Whittington and Close, 1970), and bleomycin, which required the presence of oxygen and ferric ions to react (Crooke and Bradner, 1976). A particularly important development in DNA-reactive drugs came with the discovery of cisplatin, which had its origins in the chance observation that bacterial growth was inhibited around one of the platinum electrodes of an electrophoresis apparatus containing ammonium chloride in the buffer (Rosenberg et al., 1965). Platination of DNA became a new mode of DNA damage induction and formed the basis for developing new analogues of cisplatin with reduced host toxicity.

D. Inhibitors of DNA Replication

A consequence of the elucidation of the structure of DNA was the rational design of analogues of the DNA bases, which were hypothesized to exert their anticancer activity by disruption of DNA replication. These included the thymine analogue 5-fluorouracil (Heidelberger et al., 1957) and the purine analogues 6-mercaptopurine and 8-azaguaine (Hitchings and Elion, 1954). The cytotoxic effects of aminopterin and methotrexate were traced to their inhibition, through their
effect on the enzyme dihydrofolate reductase, of the conversion of deoxyuridine monophosphate to thymidine monophosphate. The phenomenon of “thymineless death,” whereby bacteria unable to synthesize the DNA base thymine died in its absence, was found to have a parallel in mammalian cells and shaped the rationale for the development of the antimetabolite class of drugs. As the individual enzymes responsible for DNA replication were identified it became clear that the successful operation of the DNA replicase complex relied on a constant supply of the triphosphate precursors of DNA and that interruption of this supply resulted in damage to newly synthesized DNA. Natural products also played a role in the development of anticancer drugs acting on DNA replication. Arabinose nucleosides from the sponge Cryptothelya were found to have experimental antitumor activity, and one of them, the antimetabolite cytosine arabinoside, has found extensive use in the treatment of persons with leukemia (Ellison et al., 1968). The testing of chemical analogues of cytosine arabinoside led more recently to drugs such as gemcitabine, which has activity against carcinoma (Plunkett et al., 1996).

E. DNA Topology as a Target for Drug Development

In the 1960s, two logical problems concerning DNA structure became evident. The first was that the unwinding of DNA associated with DNA replication appeared to be thermodynamically impossible in the time frame involved, since the average chromosome would have tens of millions of helical twists. The second, familiar to anyone who has tried to untangle a fishing line, was that the separation of daughter DNA strands produced by DNA replication, prior to cell division, was thermodynamically impossible. Closed circular duplex DNA in some bacterial and mammalian viruses provided smaller molecular weight models for the study of these problems. Such DNA was found to exist in several distinct forms, each with the same sequence but with a different number of helical twists, and these were called topoisomers, based on topology (the branch of mathematics dealing with such differences in shape). In 1976, a new ATP-requiring enzyme, DNA gyrase, with the property of being able to change the topology of closed circular duplex DNA, was discovered in bacterial cells (Gellert et al., 1976). DNA gyrase was found to have an essential role in DNA replication, and because it could pass one strand of DNA through another, it elegantly solved the problems of how DNA could be rapidly unwound during replication and how the daughter DNA strands could be separated after replication. Subsequent studies of mammalian cells demonstrated two main classes of enzymes. The first, topoisomerase I, changed DNA topology by breaking and rejoining a single DNA strand (Been and Champoux, 1980). The second, topoisomerase II, with some of the characteristics of bacterial gyrase, broke both strands of one double-stranded DNA to allow passage of a second double-helical strand through the breakage point (Miller et al., 1981).

The discovery of the DNA topoisomerases also solved a problem concerning the activity of a number of natural products with anticancer activity that caused DNA damage but did not appear to react chemically. Actinomycin D, identified from Streptomyces cultures, found extensive early clinical use particularly in pediatric tumors (Farber et al., 1960) and was found to bind DNA by intercalating its polycyclic chromophore between the base pairs of the DNA double helix (Müller and Crothers, 1968). It was of great biochemical interest because of its potent inhibition of RNA synthesis, but this did not appear to explain its antitumor activity. Subsequently, two anthracycline derivatives, daunorubicin and doxorubicin, were also found to bind DNA by intercalation of their chromophores, but their effects on RNA synthesis were less than those of actinomycin D. The clinical activity of daunorubicin was generally confined to hematologic malignancies but that of doxorubicin was broader (Arcamone, 1985). The synthetic compound amsacrine, which had clinical activity against acute leukemia (Arlin, 1989), bound DNA by intercalation of its acridine chromophore (Wilson et al., 1981) but had little or no effect on RNA synthesis. Both amsacrine and doxorubicin were found to induce covalent links between DNA and proteins (Zwelling et al., 1981), and subsequent work demonstrated that this protein was in fact the enzyme topoisomerase II (Nelson et al., 1984). The drugs acted as poisons of this enzyme, subverting its normal function to one of inducing DNA damage.

A parallel development in plant natural product research provided podophyllotoxin analogues derived from the mandrake root (Stahelin and Von Wartburg, 1991). Podophyllotoxin itself, like colchicine, bound to tubulin, but some semisynthetic glycosidic derivatives, termed epipodophyllotoxins, were found to have superior experimental antitumor activity to podophyllotoxin itself. Etoposide, first tested clinically in 1971, was found to be useful against a variety of malignancies (Issell and Crooke, 1979). Investigation of the action of etoposide and of the related drug teniposide revealed that they had reduced binding to tubulin but induced DNA damage and poisoned the enzyme topoisomerase II. The plant product camptothecin, which did not bind DNA and previously had no known function, was found to be a specific poison for topoisomerase I (Hsiang et al., 1985). Water-soluble analogues of camptothecin, such as topotecan and irinotecan, have clinical potential, and topoisomerase I is now an established tumor target (Pommier, 1993).

F. The Search for Selectivity

While the selectivity of radiotherapy was progressively increased by localization of the radiation field to specific areas
of tumor growth, the selectivity of cytotoxic therapy was dependent on particular properties of cancer tissue. The use of microbial models gave rise to the important concept that alkylating drugs killed cells in an exponential fashion, with a certain percentage of the cell population killed with each dose (Pittillo et al., 1965). For some drugs, cytotoxicity was found to be maximal at a particular phase of the cell cycle. Skipper and colleagues (Skipper, 1967) used animal models to select administration schedules with optimal cytotoxicity for the cell-cycle-selective agents, and drug combination schedules that allowed optimal intensity of treatment. The spacing between treatments and the rate of appearance of resistant populations could make the difference between success and failure of treatment (Carl, 1989). Such reasoning was applied with success to hematologic malignancies, which often had a high rate of cell division, but was less successful in the management of solid tumors.

Another basis for selectivity was to exploit an enzyme or drug transport mechanism that was present to a different extent in tumor and normal cells. Many antimetabolites were found to exert their selectivity by such mechanisms. Topoisomerase enzymes provided a particularly good example of such selectivity since high cellular activity, which tended to occur in rapidly dividing cell populations, was associated with greater sensitivity to topoisomerase-directed anticancer drugs (Pommier, 1993). More recently, selectivity has been generated by the development of prodrugs, which have no cytotoxicity until an enzyme or other agent activates them. Initially, naturally occurring cellular enzymes, such as nitroreductases, were considered as candidates for activating prodrugs, but more recently the concept of introducing a different activating enzyme by means of a localizing antibody or gene therapy has been investigated. These concepts are discussed in Chapters 8 and 11.

3. Growth Control Pathways

While cytotoxic agents dominated the development of clinical cancer chemotherapy, the alternative approach of altering the signals that determine cancer growth was not forgotten. The demonstration by Beatson in 1896 of the role of estrogen in the progression of some types of breast cancer raised the question of whether the growth of all cancer types might be controlled by circulating hormones. Subsequent surgical studies showed that, apart from the case of prostate cancer, removal of endocrine glands was generally ineffective in cancer treatment. It was another 30 years before estrogen, one of the main hormones accounting for Beatson’s result, was identified (Frank et al., 1925), but the biochemical pathways linking steroid hormones to cell growth stimulation remained a mystery. During the 1960s and 1970s, studies of cultured cells, both normal and tumor, indicated that a diverse series of polypeptide growth factors were essential for cell growth, many specific for certain tissue types (reviewed by James and Bradshaw, 1984). An understanding of the action of such factors first required the elucidation of the molecular mechanism of regulation DNA replication and cell division.

A. The Cell Cycle Clock

One of the most fascinating questions posed by dividing normal and cancer cells was the nature of the molecular clock that instructed the cell as to when it would replicate its DNA and when it would divide. Early studies of cancer tissue identified mitotic cells by their morphology and DNA-synthesizing (S-phase) cells by their uptake of tritium-labeled thymidine, and these phases were found to be separated by periods of cell enlargement, termed G1 and G2 phase (reviewed by Tannock, 1978). The first clues to the nature of the oscillator that ran the molecular clock were provided by the discovery in developing sea urchin eggs of a protein termed cyclin. The cellular concentration of this protein increased up to the time of cell division and then abruptly decreased (Evans et al., 1983). Studies of the division of fertilized frog eggs also indicated the presence of a cyclin, the synthesis of which was necessary to cell division (Cross et al., 1989). A second component of the clock was identified from two lines of research, one using frog embryos and one using yeast mutants (Cross et al., 1989). A specific enzyme, termed a cyclin-dependent kinase (cdk), was found both to associate physically with a cyclin and to be activated by it, providing a link between the oscillator and the actuator. Several distinct cdk’s and cyclins were found to be present in mammalian cells. A third component of the clock mechanism was a protease (in the form of a proteasome) that was responsible for the degradation of the cyclin and thus the resetting of the clock (Glotzer et al., 1991; King et al., 1996). In the general scheme of the cell cycle (Fig. 2), the multiple functions required for cell division and DNA replication are exquisitely coordinated by cdk’s 1 and 2, respectively, each activated at the appropriate time by specific associated cyclins. The cell cycle time for human tumors varies from around 2 days to several weeks (Wilson et al., 1988).

B. Stopping and Starting the Cell Cycle Clock

While the majority of the body’s cells are in a nondividing state, certain cells, such as blood cell precursors in the bone marrow and epithelial cells in the gut, are capable of dividing rapidly. Some mechanism must therefore regulate the passage of cells from a quiescent state to a dividing state. Most early studies utilized cultured fibroblasts to investigate this process. Time-lapse studies (Smith and Martin, 1973) indicated that the commitment to DNA replication and mitosis was determined by a stochastic (random) mechanism, and a
“restriction point” in the G1 phase of the cell cycle was defined (Pardee, 1974), past which cells were irreversibly committed. A clear requirement was established for the presence of external polypeptide growth factors to allow passage of cells past the restriction point. Such factors were found to interact with membrane-bound surface receptors on target cells, and by the end of the 1970s it was established that at least some of these receptors, including that for epidermal growth factor, became phosphorylated as a consequence of growth factor engagement (Carpenter et al., 1979). Internal cellular proteins were also phosphorylated in response to growth factors, but the identification of the complex linkages between growth factor receptors and commitment to DNA replication and cell division required new findings.

A major step forward in the identification of the pathway for initiation of cell growth had its origins in Peyton Rous’s study of cancer-causing viruses in birds, mice, and rats in the early part of the 20th century (Rous, 1983). In 1983, the extraordinary finding was made that a gene in a transforming virus of simian apes was similar or identical to the transforming virus of simian apes (Rous, 1983). In 1983, the extraordinary finding was made that a gene in a tumor-transforming virus of simian apes was similar or identical to that specifying a known growth factor for cultured cells (Doolittle et al., 1983; Waterfield et al., 1983). Subsequent work defined a variety of genes that could be transmitted by retroviruses to the tissue of a variety of birds and animals, causing a tumorigenic change. As the functions of these corresponding gene products were elucidated, it was found that they mapped to biochemical pathways linking the binding of growth factors to the commitment of cells to DNA replication and cell division.

The above work led to identification not only of a network of regulatory proteins but also of new cyclins (D-cyclins) and cdk’s (4 and 6) that control the passage of the cell from a quiescent phase into the cell cycle. The retinoblastoma protein and the transcription factors E2F and c-myc were also implicated in a complex control system that resulted in the up-regulation of the E and A cyclins and subsequent initiation of DNA replication.

As the elements of this control system were identified, it also became clear that the function of one or more of these elements was defective in cancer. For instance, many human cancers were found to be associated with a mutated ras oncogene such that the cells behaved as though they were being continuously stimulated by growth factors (Pronk and Bos, 1994). Furthermore, many cancer cells lacked the proper function of proteins, such as the retinoblastoma protein, that regulated entry into S phase (Herwig and Strauss, 1997).

C. Programmed Cell Death

In 1972, a pivotal hypothesis was advanced that cell death was, like progress through the cell cycle, a product of precise cellular programming (Kerr et al., 1972). This hypothesis was to have a profound effect not only in explaining the loss of cells during the development of the embryo but in advancing our understanding of cancer growth. Apoptosis was found to be an energy-dependent process whereby a cell was converted to fragments that could be absorbed by surrounding tissue without the initiation of an inflammatory response (Wyllie, 1993). The molecular mechanisms of apoptosis are described in Chapter 4.

In a multicellular organism, loss of a single cell is generally unimportant. On the other hand, loss of growth control in a single cell could lead, in the absence of any protective mechanism, to unrestricted and catastrophic growth. The body appears to have a protective mechanism to ensure that any such cells losing growth control are eliminated. The mechanistic links are not yet fully defined, but transcription factors such as E2F and c-myc, which are involved in driving cells into the cell cycle, are also involved in driving cells into apoptosis (Evan and Littlewood, 1998; King and Cidlowski, 1998). Thus, cancer growth is a balance between cell birth and cell death, each initiated by the same pathway (Fig. 3). Cancer cells (as well as normal cells) can be prevented from undergoing apoptosis by so-called survival factors (Evan and Littlewood, 1998), such as insulin-like growth factor 1 (Juin et al., 1999) and cell–matrix interactions (Meredith et al., 1993).

D. The Cell Cycle Calendar

The pioneering studies of Hayflick showed that when human fibroblasts were cultured, they would die after a certain...
number of generations by a process called senescence (Hayflick and Moorhead, 1961; Hayflick, 1965). The number of generations of doublings, typically 60–80 for fetal cells, progressively reduced as the age of the donor of the fibroblasts increased, suggesting that some kind of calendar was running during the lifetime of an individual cell. More recently, evidence for a slightly different calendar mechanism has been obtained in breast epithelial cells (Romanov et al., 2001).

Tumor cells in culture, in contrast to normal cells, appeared to grow indefinitely, suggesting that the lack of a functioning calendar may be a common characteristic (Goldstein, 1990). An understanding of the mechanism behind the calendar was provided by research on the question of how a linear chromosome could be replicated. Characterization of the DNA replication machinery indicated that DNA polymerase had to start from a priming strand, either DNA or RNA, bound to a DNA strand in a duplex conformation (Lingner et al., 1995). Thus, DNA polymerase could not replicate the ends of chromosomes, and with each successive round of DNA replication the chromosomes would become progressively shorter. The solution to this “end-replication” problem was provided by the discovery of the enzyme telomerase, which added repetitive sequences to the ends or telomeres of chromosomes (Morin, 1989). Normal tissues, unlike embryonic tissues, generally lack telomerase activity. Thus, loss of telomeric DNA sequences might provide a mechanism to ensure that cells that mutate to allow inappropriate cell division, even if not killed directly by apoptosis, die as a result of telomeric DNA loss. It appears that the acquisition of an active telomerase is a very common feature of cancer tissue (Kim et al., 1994).

E. Therapeutic Possibilities

One of the earliest therapeutic successes in cell growth control was the discovery of triphenylethylene derivatives that antagonized the effects of estrogens (Ward, 1973). These so-called antiestrogens revolutionized the management of some types of breast cancer. The basis for the antitumor action of antiestrogens is complex and multifactorial. Estrogen was found to bind to an internal protein that acted as a transcription factor (McKnight et al., 1975), and further work indicated that the products of transcription had multiple effects on target cells, including changes in the expression of growth factor receptors (Curtis et al., 1996). Thus, one possible mechanism of action of the antiestrogens is to decrease the action of survival factors and thus increase the rate of cell death.

More recently, research suggesting that cancer growth represents a balance between cell birth and cell death suggested new approaches. Thus, either a drug-induced decrease in cell birth rate or an increase in cell death rate might result in tumor regression. Low-molecular-weight drugs have been developed that either reduce the progress of cells through the cell cycle, thereby decreasing the cell birth rate, or increase the rate of apoptosis. One important consequence of this research was the finding that cytotoxic drugs, discussed in earlier sections of this chapter, could increase the rate of apoptosis. Cisplatin was one of the first cytotoxic drugs demonstrated to induce cultured cells to undergo apoptosis (Barry et al., 1990). Damaged DNA appears to activate specific enzymes, such as Ataxia Telangiectasia Mutated (ATM) kinase, which in turn initiate the series of steps leading to apoptosis (Meyn, 1995). This topic is further discussed in Chapters 2–4.

The reinstatement of cancer cell mortality constitutes another possible therapeutic approach to cancer treatment. If the “calendar” could be reactivated, such as by inactivation of telomerase activity, cancer cells might once again have a finite lifetime. The design of therapies aimed at inhibiting telomerase activity is still at an early stage and has not been reviewed specifically in this volume. However, a number of excellent reviews can be found (Neidle and Kelland, 1999; Perry and Jenkins Thomas, 1999).

4. Host–Tumor Interactions

Cancer cells do not exist as isolated units but as components of a tissue containing both host and tumor cells. Host cells not only provide, through the vascular endothelium, the precursors of cancer cell growth but also secrete factors that have profound effects on the life and death of tumor cells. The early finding that a mixture of bacterial exotoxins and endotoxins present in “Coley’s toxins” were effective in some types of cancer, particularly lymphomas and sarcomas (reviewed by Wieman and Starnes, 1994), prepared the way for
both vascular and immune approaches to the treatment of patients with cancer (Pardoll, 1993). Early studies of the action of bacterial lipopolysaccharides in mice led to the discovery of their induced effects on tumor capillaries, leading to vascular collapse and tumor necrosis (Algire et al., 1947). Based on these results, a variety of clinical studies using nonspecific immune stimulants such as Corynebacterium parvum and bacillus Calmette-Guérin were instituted (reviewed by Mathé et al., 1973). In the 1960s, polypeptides were identified that stimulated the proliferation of various types of blood cells (Metcalf, 1971). This was followed by the identification of cytokines that mediated the communication between cells in the immune system and other types of cells. One of these cytokines, a protein termed tumor necrosis factor (TNF), was found to mediate the effects of bacterial toxins (Carswell et al., 1975), acting on capillaries to increase their permeability and induce their collapse (Watanabe et al., 1975), leading ultimately to increased tumor cell death. Some of the pathways involved in the complex interactions are shown in Figure 4.

### A. Low-Molecular-Weight Inducers of Tumor Necrosis

One of the first reports on the antitumor activity of colchicine described the induction of necrosis in transplantable solid tumors. The similarity of the histologic changes to those caused by administration of bacterial toxins suggested an effect on the tumor vasculature (Ludford, 1945). Subsequently, the synthetic drug flavone acetic acid, the antibiotic fostriecin, and the plant product homoharringtonine were also found to induce hemorrhagic necrosis of experimental tumors (Baguley et al., 1989). Apart from colchicine, a variety of tubulin binders, including podophyllotoxin, vincristine, vinblastine, and combretastatin, were found to induce tumor necrosis (Baguley et al., 1991; Hill et al., 1993; Dark et al., 1997). Flavone acetic acid and the structurally related 5,6-dimethylxanthone-4-acetic acid appeared to act as a consequence of local production of TNF (Mace et al., 1990; Zwi et al., 1994), while the mitotic inhibitors appeared to change the shape of vascular endothelial cells (Dark et al., 1997).

One particularly important class of tumor–host interactions concerns the vascular endothelial cells that provide the blood supply to tumors. Measurement of the proliferation rates of vascular endothelial cells in tumors showed them to divide more rapidly than in normal tissues (Hobson and Denekamp, 1984), leading to antivascular strategies for tumor management (Denekamp, 1990). At the same time, the factors responsible for tumor angiogenesis were being elucidated, and a basis for antiangiogenic drugs for cancer treatment was formulated (Folkman, 1985). This is discussed in Chapter 7.

### B. Low-Molecular-Weight Modulators of Cytokine Effects

Research on cytokines led not only to clinical trials of individual cytokines but to the development of low-molecular-weight compounds that might modulate cytokine production. The anthelminthic drug levamisole was initially investigated as an immunostimulant (Amery et al., 1977), has found clinical use in the treatment of colon and other tumors, and is currently thought to act by changing the balance of cytokine actions (Szeto et al., 2000). Tilorone, a low-molecular-weight inducer of interferon (Zschiesche et al., 1978), has been tested in phase II anticancer trials (Cummings et al., 1981). Muramyl dipeptide was investigated as a low-molecular-weight inducer of TNF and appeared to act in concert with endotoxin to induce antitumor effects (Bloksma et al., 1985). Thalidomide, infamous for its teratogenic effects in humans, was found to inhibit the synthesis of TNF (Sampaio et al., 1991) and, more recently, has shown promising activity in the management of multiple myeloma (Singhal et al., 1999). A complete understanding of how cytokine-modulating drugs act on tumor tissue requires further research.

### 5. Conclusions

In many ways, the scientific objectives of research into the drug-mediated treatment of cancer have not changed over the
last few decades. We still search for selective poisons for cancer cells, we still wish to change, selectively, the regulation of growth of cancer cells, and we still wish to encourage the body’s normal tissues to reject cancer tissue. While the incidence of radically new ideas in cancer treatment is relatively sparse, our understanding of the molecular makeup of the cancer cell has changed dramatically and the available technology is extraordinarily different. For instance, recent studies using microarray technology combined with the sequencing of the human genome provide the potential to investigate the activity of huge numbers of genes in response to anticancer agents (Scherf et al., 2000). The challenge is to devise, from a deep understanding of the action of known anticancer drugs on human cancers, new strategies for cancer treatment.

References


