Drug Development in Solid Tumors: Personal Perspective of Dr. Emil J Freireich’s Contributions

Paul P. Carbone
University of Wisconsin Comprehensive Cancer Center and Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin 53792

Abstract
The development of chemotherapy for patients with the major cancers progressed from the initial success attained in the treatment of acute leukemias and choriocarcinoma. Many of the principles of therapy were based on the concepts developed in the experimental laboratories and early clinical studies done at the NIH Clinical Center and other centers around the country.

The purpose of this review is to describe some of the early advances in cancer therapy and show how many are based on the efforts of Dr. Emil J Freireich. Over his career, Dr. Freireich has published more than 500 papers and worked on more than 70 different drugs and combinations. The principles defined by Dr. Freireich, namely, the use of intermittent intensive chemotherapy to induce complete remissions (CRs), intensification of therapy in remission, and the use of unmaintained remissions to assess cure, have been important in developing curative chemotherapy programs in patients with acute leukemias.

These same principles were applied to combination therapy of Hodgkin’s disease as the nitrogen mustard, vincristine, procarbazine, and prednisone combination was developed. This led to the high CR and cure rate for this disease. The treatment of metastatic breast cancer does not produce a high proportion of CRs, and cures of metastatic disease are unlikely with chemotherapy alone. But adjuvant chemotherapy after surgery has resulted in a significant reduction in cancer mortality. Many challenges remain in increasing the cure rate for the major solid tumors. New avenues of controlling cell growth and metastases need to be explored. One approach that is exploitable is the use of drugs or nutrients to prevent cancer. Laboratory approaches are now becoming a clinical reality.

Introduction
It is my pleasure to participate in honoring one of the most innovative figures in oncology in the United States, Dr. Emil J Freireich. Since 1960, when I first went to the NIH as a staff investigator, I have had the pleasure and, sometimes, anxiety of meeting with J to discuss issues related to oncology. Walking into his office after 4 p.m. meant that you could plan on prolonged and heated discussions. I had the feeling that, no matter what you discussed, he took the opposite tack with a strong and loud position. Few antagonists have been as knowledgeable and intelligent as J. To dispute J requires knowledge and fortitude.

My paper is divided into four parts. First, I provide a brief historical perspective of how cancer drugs and principles of treatment for the bulk of cancers that are not characterized as leukemia were developed. Second, I highlight the enormous number of chemotherapeutic agents and the conceptual contributions that Dr. Freireich has added to the field of treatment of cancers, including both hematological and solid tumors. Third, I describe, in some detail, two aspects of advances to the field of oncology that I have been associated with and for which I owe a debt to Dr. Freireich and some of our colleagues at the NCI. Finally, I comment on what I see as an important future direction for the control of solid tumor cancers.

Historical Perspective
The treatment of cancer with drugs dates back to the 19th century and the use of potassium arsenite (1). However, modern cancer chemotherapy became a reality in 1942, when Gilman and coworkers (2) initiated the first clinical trial of NM at Yale University. Following this first report of dramatic responses in lymphomas with NM, the search was on to develop other alkylating agents with anticancer effects. Other agents were developed, but little evidence was found to suggest that one alkylating agent was significantly better than another. Some differences were found that were related to oral effectiveness, CNS penetration, or sparing of platelets, but no major defined therapeutic advantage was seen for one drug over another. Cyclophosphamide, developed in the 1950s, has become the most commonly used alkylating agent (3).

Hormone therapy to treat several major common cancers dates back to the 19th century and the removal of ovaries by Beatson (4), who demonstrated that regression of breast tumors followed. Modern use of estrogens, androgens, and other oral hormonal agents resurfaced in the mid-1940s (5). The introduc-
tion of the antiestrogen tamoxifen (6), the aromatase inhibitor aminoglutethimide (7), and the luteinizing hormone-releasing hormone inhibitors (8) in the 1970s and 1980s decreased, if not eliminated, the need for extirpative endocrine surgeries.

Aminopterin, a folic acid antagonist, was initially found to be effective in acute leukemia of children by Farber et al. (9). MTX was developed in 1948 and replaced aminopterin because of its better therapeutic index in L-1210 leukemia in mice (10). In 1961, Li and colleagues (11) at NIH reported the cure of choriocarcinoma with MTX. This was the first demonstration of a cure of a solid tumor by chemotherapy. The cure was facilitated by a responsive tumor and by the sensitivity of tumor cell numbers as an indicator. Treatment was dictated by the persistence of measurable human chorionic gonadotrophin rather than by the clinical disappearance of tumor. The persistence of the marker clearly indicated the need to continue treatment beyond clinical remission (12). A continued rise in the human chorionic gonadotropin marker also indicated the development of drug resistance and the need to change therapy.

About the same time at the University of Wisconsin, Heidelberger et al. (13) synthesized FU, a pyrimidine analogue. Clinical investigators at the University of Wisconsin showed that this drug had activity against gastrointestinal, breast, and head and neck cancers (14). It is of interest that, in the Lugano conference proceedings in 1964, only choriocarcinoma, acute leukemia, Wilms’ tumor, and retinoblastoma were considered curable by chemotherapy (15). Benefits to lymphomas, testicular cancer, breast cancer, ovarian cancer, and prostate cancer were described, but these benefits were not lasting.

The search for anticancer drugs in the 1970s uncovered a variety of new agents, such as the Vinca alkaloids (16, 17), procarbazine (18, 19), anthracyclines (20, 21), and platinol (22, 23). Activity of these drugs was seen in lymphomas and breast, ovarian, germ cell, and small cell lung cancers. But these tumors were not cured by administration of single agents. In the 1990s, the taxanes (24) and the topoisomerase inhibitors (25) were discovered. At present, there are more than 100 agents with activity against one cancer or another. In addition, a wide variety of biologicals, including cytokines, immune stimulants, antibodies, and growth factors, are now available for clinical research therapies. These new agents are used as supportive therapies and diagnostic agents, as well as treatments.

From 1952 until the 1980s, the search for new agents and the preclinical testing of these compounds were major responsibilities of the NCI. Not only was a drug-screening component established at the NCI, but in 1955, several national clinical trials groups were established to test these compounds. Thus, the conceptual and scientific development of these drugs was the work of investigators like Drs. Freireich, Frei, Holland, Lasagna, Chalmers, Moore, Zubrod, Jones, and others. These investigators, as well as many others in national cooperative groups, led the way to modern chemotherapy (26). The cooperative groups formulated the standards for protocols, response definitions, performance status, and analysis methods. Skipper et al. (27), Goldin et al. (28), Bruce et al. (29), and others defined the conceptual and experimental bases of chemotherapy, including quantitative tumor kinetics, cell survival curves, schedule dependency, adjuvant therapy, and combination chemotherapy. Some of these concepts will be referred to again later in this paper.

The Freireich Contributions

Over the years, Dr. Freireich and his trainees have made many important contributions to the management and control of leukemia. I would like to focus on two aspects of his contributions. The first relates to the development of anticancer drugs. In reviewing Dr. Freireich’s more than 500 published papers, I counted at least 70 drugs or combination chemotherapies that Dr. Freireich and his colleagues were instrumental in developing or demonstrating their effectiveness. The cumulative plot of these agents is shown in Fig. 1. The list of drugs and combinations is gleaned from Dr. Freireich's publications. The list is impressive. These include single agents such as vincristine (30), 1-B-D-arabinofuranosylcytosine (31), fludarabine (32), asparaginase (33), methyl glyoxal-bis-guanilhydrazone (34), hydroxyurea (35), duanorubicin (36), IFN-γ (37), and 2-chlorodeoxyadenosine (38). In addition, he and his colleagues demonstrated in patients with leukemia that combination chemotherapy was able to cure children with acute leukemia (39).

A second aspect of Dr. Freireich’s contributions focuses on the major conceptual advances that relate to the treatment of solid tumors he and his colleagues have promulgated over the years (Table 1). This list includes major contributions to the concepts of combination chemotherapy, supportive care, blood component support, hematopoietic transplantation, immunology, immunotherapy, neoplastic meningitis, cytogenetic correlates of disease and response to therapy, and approaches to improving remission duration. He was a pioneer in the development of therapies for CNS neoplastic disease and investigating the basic pharmacology of several agents in the CNS.

Dr. Freireich was among the first to study why patients with acute leukemia die and to devise approaches to overcome these obstacles (40). He realized the fact that the leukemia cells could be eradicated and that the limiting factor might be the
host. His contributions to supportive care and component replacement of platelets and WBCs are also monumental. These have led to the development of the cell separator and peripheral stem cell separation. Among these contributions, one of the most significant, in my opinion, was Dr. Freireich’s concept that cures of cancer could be demonstrated by assessing unmaintained remissions following combination chemotherapy and intensification during remission (12). This principle was instrumental in the design of curative MOPP trials in patients with lymphomas.

**Successful Therapy Regimens in Lymphoma and Breast Cancer**

The principles of combination chemotherapy were worked out over the years in the laboratory by Skipper *et al.* (27), Sartorelli and Creasy (41), and Frei (Ref. 42; Table 2). These principles were first applied clinically by Dr. Freireich and his colleagues in the treatment of acute leukemia in 1962 (39). The combinations VAMP and POMP were reported to have high remission rates in acute leukocytic leukemia (43). These regimens contained multiple agents with activity against leukemia, given at high doses, intermittently to allow for host recovery. He also appreciated the fact that stopping therapy at the time of CR would not be as curative as adding additional therapies during remission (late intensification) and then stopping. As I mentioned, the real key to defining success, according to Dr. Freireich, was that, not only did one need to use combination chemotherapy and intensification treatment in remission, but one also needed to stop therapy and follow the patients off therapy to eventually get an assessment of cell cure (Table 2).

We and others had shown that a variety of single agents were effective in producing remissions in patients with lymphoma (17, 44). However, these remissions were rarely complete, and they lasted only a few months. Lacher and Durant (45) had shown a high remission rate of combinations using velban and chlorambucil. By 1967, cytoxan, MTX, vincristine, and prednisone were shown to be active in producing mainly partial remissions in subjects with Hodgkin’s disease, alone and in combination with radiation (46). The chemotherapy regimen is shown in Table 3. As far as I remember, this protocol was never activated. Like the other earlier study, all stages of patients with Hodgkin’s were eligible for study (47). Stage I and II patients also received 4000 rad to clinically involved fields. This protocol produced 80% CRs in 14 patients, 12 of whom were previously untreated (46, 48). Only five patients had Stage III disease and were treated with four-drug combination alone. All of these patients achieved CRs.

After this initial success, a second combination protocol was developed at the NCI replacing MTX with procarbazine in the cytoxan, vincristine, and prednisone combination (Table 3). Again, radiotherapy was to be given to patients with localized disease (Stage I and II). The drug schedules and doses are seen in Table 3. As far as I remember, this protocol was never activated. Like the other earlier study, all stages of patients with Hodgkin’s disease were eligible, and treatment was given for three 2-week cycles. This study was never activated because several key individuals involved in the original study left NCI.

The final combination, MOPP, protocol (Table 3) for combination chemotherapy was developed in 1967. It took advantage of several recent observations. One was that NM was found to produce a higher response rate than did cytoxan in a comparative study of alkylating agents in lymphoma patients (49). NM was therefore substituted for cytoxan. The number of cycles of chemotherapy

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**Table 1** Major conceptual advances developed by Dr. Freireich and his colleagues

<table>
<thead>
<tr>
<th>Conceptual advance</th>
<th>Solid tumor relevance</th>
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</thead>
<tbody>
<tr>
<td>Nonrandomized clinical trials (92)</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Intracranial blastic lesions (93)</td>
<td>CNS metastases</td>
</tr>
<tr>
<td>Sequential vs simultaneous combination chemotherapy (94)</td>
<td>Combination chemotherapy</td>
</tr>
<tr>
<td>Using mg/m² as reference for dosing for chemotherapy (95)</td>
<td>Chemotherapy of children and adults</td>
</tr>
<tr>
<td>CNS leukemia (96)</td>
<td>Meningeal carcinomatosis</td>
</tr>
<tr>
<td>Intrahepatic chemotherapy (97)</td>
<td>Meningeal carcinomatosis</td>
</tr>
<tr>
<td>Use of cytogentic to diagnose relapse (98)</td>
<td>Minimal disease assessment</td>
</tr>
<tr>
<td>Cyogenetic characterization of acute leukemia (99)</td>
<td>Molecular biology of cancer</td>
</tr>
<tr>
<td>RBC homograft following peripheral blood transfusions (100)</td>
<td>Peripheral stem cell transfusions</td>
</tr>
<tr>
<td>Stem cells in peripheral blood (101)</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Platelet count and bleeding (102)</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Plasmapheresis for platelets (103)</td>
<td>Supportive care, immunotherapy</td>
</tr>
<tr>
<td>Leukopheresis machine (104)</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Protected environments (105)</td>
<td>Supportive care</td>
</tr>
<tr>
<td>WBC level and infections (106)</td>
<td>Treatment</td>
</tr>
<tr>
<td>WBC transfusions (107)</td>
<td>Treatment</td>
</tr>
<tr>
<td>Late intensification of remission in acute leukemia (108)</td>
<td>Treatment</td>
</tr>
<tr>
<td>Cell population kinetics and chemotherapy (39)</td>
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</tr>
</tbody>
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**Table 2** Principles of combination therapy and Freireich principles of defining curative therapy

<table>
<thead>
<tr>
<th>Principles of combination therapy</th>
<th>Freireich principles of curative therapy</th>
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<tbody>
<tr>
<td>Effective agents as single drugs</td>
<td>Combination chemotherapy using full doses</td>
</tr>
<tr>
<td>Agents with different mechanisms of action</td>
<td>Intermittent treatment to allow for host recovery</td>
</tr>
<tr>
<td>Use of each agent at optimal dose</td>
<td>Treatment beyond complete remission</td>
</tr>
<tr>
<td>Use of the drugs intermittently</td>
<td>Patients followed in unmaintained remission</td>
</tr>
<tr>
<td>Agents with different limiting toxicities</td>
<td></td>
</tr>
</tbody>
</table>

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classification, Stage I, II, and III patients with treated and untreated Hodgkin's were eligible for study (47). Stage I and IIA patients also received 4000 rad to clinically involved fields. This protocol produced 80% CRs in 14 patients, 12 of whom were previously untreated (46, 48). Only five patients had Stage III disease and were treated with four-drug combination alone. All of these patients achieved CRs.
Table 3  COMP combination chemotherapy, COPP combination chemotherapy for Hodgkin’s disease, and MOPP combination chemotherapy for Hodgkin’s disease

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Schedule</th>
</tr>
</thead>
</table>
| COMP<sup>a</sup> | Cyclophosphamide 660/m², i.v., days 1 and 8  
MTX 35 mg/m², i.v., days 1, 4, 7, 11  
Vincristine 1.2 mg/m², i.v., days 1 and 8  
Prednisone 40 mg/m², p.o., for 84 consecutive days |
| COPP<sup>b</sup> | Cyclophosphamide 600/m², i.v., days 1 and 8  
Vincristine 1.2 mg/m², i.v., days 1 and 8  
Procarbazine 150 mg/m², p.o. daily, 14 days  
Prednisone 40 mg/m², p.o., 14 days |
| MOPP<sup>c</sup> | NM 1.4 mg/m², i.v., days 1 and 8  
Vincristine 1.2 mg/m², i.v., days 1 and 8  
Procarbazine 150 mg/m², p.o. daily, 14 days  
Prednisone 40 mg/m², p.o., 14 days<sup>d</sup> |

<sup>a</sup> Cycles were repeated three times, separated by 10 days. Total duration was 84 days (48).  
<sup>b</sup> Interval was to be a minimum of 7 days, for three courses.  
<sup>c</sup> Interval was to be 14 days, and the course was repeated for six cycles or until two cycles were given in remission.  
<sup>d</sup> Prednisone was given only during the first and fourth cycles.

was also extended to six or until the patient had two cycles beyond clinical CR. This, again, was based on the idea that we needed to go beyond the three cycles shown to produce CRs and that cell cure would require treatment beyond apparent clinical CR. The patients to be treated on this protocol were all advanced disease (Peters et al. (56), Longo and DeVita (55)). (56), Rosenberg and DeVita (55), (56), Young et al. (57), to name a few. These remissions were not sustained (58). On the basis of experimental data from Martin (59) and Schabel (60), surgical removal of the bulk of the tumor and treatment with chemotherapy or chemoimmunotherapy would be curative in mice. These animal studies showed that resistance to chemotherapy of advanced tumors was kinetic rather than pharmacological. The same drugs, when used after debulking or early after systemic administration, would be curative, but when used with bulky or advanced cancers in mice, they would not be effective. The experimental basis for surgical adjuvant therapy is summarized in Fig. 2, using the Lewis lung cancer model (61). Surgery is used to resect primary tumors, and chemotherapy is used to treat systemic disease. Surgery alone or chemotherapy alone was not effective.

Early attempts at adjuvant therapy by Nissen-Meyer et al. (62) with single-agent cytoxan and by the NSABP with thiopeta and FU did not result in major benefits compared to surgery alone (63). Trials with perioperative chemotherapy were not showing any added sustained benefit. However, one major problem with these adjuvant therapy trials was that they were based on the concept that chemotherapy needed to be given at the time of or shortly after surgery to kill the circulating tumor cells that were dispersed at the time of surgery. Accordingly, the long-term results were disappointing, although some analyses did demonstrate survival differences for subsets of patients. In retrospect, the principles derived from the laboratory and the leukemias were not being applied to the early adjuvant trials.

By 1970, combination chemotherapy for breast cancer had begun to diverge along two different lines. One was a continuous daily treatment program proposed by Dr. Cooper of Buffalo (CMFVP; Ref. 64); the other was the NCI, Medicine Branch, trial using a more intermittent schedule of CMFP (65). These treatment programs are shown in Table 4. Remissions were seen in 60–70% of the patients, with about 10% of those being CRs. These regimens formed the basis of the early combination adjuvant programs.

However, despite these interesting results, medical oncologists were not in a position to do adjuvant clinical trials. Stage I and II patients were primarily managed by surgeons, who would refer sustained remissions, even with continued therapy. Combination chemotherapy of metastatic disease patients resulted in more CRs (15–25%), but these remissions were not sustained (58). On the basis of experimental data from Martin (59) and Schabel (60), surgical removal of the bulk of the tumor and treatment with chemotherapy or chemoimmunotherapy would be curative in mice. These animal studies showed that resistance to chemotherapy of advanced tumors was kinetic rather than pharmacological. The same drugs, when used after debulking or early after systemic administration, would be curative, but when used with bulky or advanced cancers in mice, they would not be effective. The experimental basis for surgical adjuvant therapy is summarized in Fig. 2, using the Lewis lung cancer model (61). Surgery is used to resect primary tumors, and chemotherapy is used to treat systemic disease. Surgery alone or chemotherapy alone was not effective.

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Development of Solid Tumor Chemotherapy

In 1970, I was asked by senior members of ECOG to assume their chair. One of the main reasons I was interested in doing so was that I would be able to do adjuvant trials in breast cancer. In addition, I also served as Head of the Treatment Committee of the Breast Cancer Task Force (67). This was part of a larger coordinated effort of the NCI that had assigned monies and staff to stimulate specific research efforts against breast cancer. The activities of this working committee involved performing laboratory research, encouraging screening, and fostering new therapies. Some of the major achievements of this task force were: defining the role of estrogen receptors in breast cancer; fostering the early surgical trials of mastectomy, with and without radiation therapy; and comparing lumpectomy with radiation to mastectomy alone. The committee efforts did not duplicate the efforts of the Division of Cancer Treatment, but they did support key trials in surgery and the first national modern clinical trial of adjuvant therapy.

Working with Bernard Fisher, the Chairman of the NSABP, and CMF regimen (CMFVP; Ref. 64)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinca crystalline</td>
<td>0.025 mg/kg</td>
<td>Weekly</td>
<td>i.v.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.075 mg/kg</td>
<td>Daily, reducing by half every 10 days to 5 mg</td>
<td>p.o.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 mg/kg</td>
<td>Daily for 8 weeks</td>
<td>p.o.</td>
</tr>
<tr>
<td>MTX</td>
<td>0.7 mg/kg</td>
<td>Weekly for 8 weeks then every 2 weeks</td>
<td>i.v.</td>
</tr>
<tr>
<td>FU</td>
<td>12 mg/kg</td>
<td>Weekly for 8 weeks then every 2 weeks</td>
<td>i.v.</td>
</tr>
<tr>
<td>NCI CMF regimen (65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>100 mg/m²</td>
<td>Daily for 14 days</td>
<td>p.o.</td>
</tr>
<tr>
<td>MTX</td>
<td>60 mg/m²</td>
<td>Days 1 and 7</td>
<td>i.v.</td>
</tr>
<tr>
<td>FU</td>
<td>600 mg/m²</td>
<td>Days 1 and 7</td>
<td>i.v.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40 mg/m²</td>
<td>Daily for 14 days</td>
<td>p.o.</td>
</tr>
</tbody>
</table>

*a* Cycle repeated after 14-day rest period.

Patients only when they developed metastatic disease. Moreover, the toxicity of these drugs (hair loss, leukopenia, nausea and vomiting, thrombocytopenia, and mouth ulcers) made these regimens unacceptable to the surgeons and the patients.

I initiated an adjuvant study at NCI/NIH in the mid-1960s with a combination of phenylalanine mustard and FU, to be given in cycles over an 18-month period (66). However, at that time, the NIH surgeons were not seeing early breast cancer patients, and my protocol attracted only a few patients, mostly family members of NIH staff. Phenylalanine mustard was chosen because it did not cause hair loss and could be given p.o. As a single agent, it was active against breast cancer, although few CRs were achieved. Moreover, based on data from experiments in the mouse by Skipper and Schabel (60), the effectiveness of an agent was greatly caused by using those drugs. ECOG began its own tamoxifen-, Cytoxan, MTX, FU-, and cytoxan, adriamycin, FU-based trials (69).

As I mentioned above, combination chemotherapies CMF and CMFVP were shown to produce higher response rates than did single agents. However, the toxicity effects were inhibiting clinical groups from using these more intensive and effective combinations in the adjuvant setting, except for one uncontrolled study by Cooper (70). In 1973, Dr. Gianni Bonadonna, who was at the Milan Cancer Institute in Italy and had trained in medical oncology in the United States, was testing several new agents, especially doxorubicin. He expressed an interest in doing an adjuvant therapy program in node-positive patients, and we encouraged him to use the CMF regimen developed at the NCI. His trial, reported in 1976, showed that CMF was effective in premenopausal women as adjuvant therapy (71). His studies set the ground for using the CMF and, eventually, the Adriamycin combinations. The Cooper regimen was used by Cooper in an uncontrolled trial reported in 1979 and by other national cooperative groups (70, 72).

A curious result appeared in both the NSABP and Milan Cancer Institute Trials, namely, adjuvant chemotherapy in women over 50 was not showing a statistical benefit. We now know that there is a benefit of combination chemotherapy, but it was not demonstrated because of the small sample size. The large overview reports have shown a significant benefit with combination chemotherapy in the older population (73).

Although these trials were underway, tamoxifen, an antiestrogen, was being used in estrogen receptor-positive tumors. The response rate was significant. A series of adjuvant trials
looking at tamoxifen alone for 1 year and then 2 years were begun. Clinical and laboratory studies from Jordan and Tormey (74, 75) at the University of Wisconsin were showing that longer-term treatment was more tolerable and possibly more effective. This idea was tested by a large number of groups (73), demonstrating that 5 years is better than 2 years. Combinations of chemotherapy and tamoxifen also showed significant benefit. The question now arises as to whether 10 years of tamoxifen treatment is any better than 5 years.

Current approaches to adjuvant therapy are incorporating newer agents, such as Taxol (76) and taxotere (77), as well as the use of sequential combinations, stem cell support, and dose intensification. Trials are also using neoadjuvant therapy as well. However, these studies in breast cancer indicated that, unlike animal studies with rapidly growing tumors, more intensive regimens would be needed in the human cancers, in which growth rates and cell kinetics have indicated a diverse and resistant population.

**Future Therapy in Solid Tumors**

New and exciting therapies include immunotherapy, the use of cytokines and differentiating agents, and gene therapy. All of these avenues are worth exploring; however, I would like to focus my final point on developing effective chemopreventive agents, an area of personal interest. What we have seen is that most solid tumors that are metastatic are inherently or kinetically resistant to treatment with drugs. CR, defined as disappearance of all signs of cancer, is rarely achieved. The major solid tumors, when they are metastatic, do not go into long-term remissions. Even high-dose chemotherapy with stem cell replacement appears to play a limited role in curing most patients with advanced disease. What are some alternative options?

We are learning more and more about the steps in carcinogenesis. We can look for new approaches to controlling cancer by interfering with the initiation, promotion, or progression of cancer. There is also a role for these approaches in preventing secondary cancers that are caused by long-term consequences of current therapies.

In some cancers for which we know the important causative factors, *i.e.*, smoking in lung cancer, it is important for all of us to support public policy and legislative attempts to control the use of tobacco. A few cancers are clearly associated with genetic predispositions. However, most cancers do not have any known single causative factor or an inherited predisposition. Moreover, the numbers of cancers directly related to these germ-line genetic changes are few. However, many experimental systems show that one can interfere with the early steps in carcinogenesis. Whereas initiation may be a single event, progression is likely to be a series of chronic events (78). Wattenberg (79) lists more than 20 classes of agents that are known to inhibit carcinogenesis (Fig. 3).

I will briefly describe two approaches that we have explored at the University of Wisconsin. One is associated with the use of the antiestrogen tamoxifen. This drug, which was shown to be effective in blocking the binding of estrogen to the receptor, has clinical activity against both advanced and early disease (80, 81). Studies by Jordan (74) demonstrated that the induction of cancers by 7,12-dimethylbenz(a)anthracene in rats could be blocked by the administration of tamoxifen after the carcinogen (74). However, before taking this to a prevention trial, one needs information about the effects of tamoxifen on bone mineral density and cardiovascular risks. Even if tamoxifen could diminish the rate of cancers, if the antiestrogen effects resulted in an increase in heart attacks or osteoporosis, then the prevention of cancer would be for naught. A trial known as the Wisconsin Tamoxifen Study, comparing the changes in bone mineral density and serum cholesterol in postmenopausal women with early-stage breast cancer, was carried out. In 1990 and 1992, Love *et al.* (82) reported that tamoxifen improved the bone mineral density, decreased the serum cholesterol, and caused a favorable lipid profile change (83), compared to a randomized control group of women who were given a placebo. This effect has persisted for 5 years (84). Subsequently, a large national trial was funded to test this hypothesis (74, 85).

A second area of interest in chemoprevention, derived from studies at the McArdle Laboratory at the University of Wisconsin, is the use of DFMO to inhibit promotion induced polyamine production and tumor induction (78). DFMO has a specific effect on the enzyme ODC, which synthesizes polyamines from putrescine. In many experimental systems, carcinogenesis is associated with the induction of ODC and increased polyamine biosynthesis (86). This phenomenon has been known for years and appears to be a common mechanism in skin, breast, colon, bladder, prostate, and stomach cancers.

In 1985, Loprinzi *et al.* (87) developed an *in vitro* system using a 3-mm skin assay obtained by a punch biopsy to measure phorbo1 ester-induced ODC. The hypothesis was that, if a chemopreventive agent was present in sufficient concentration in the blood and tissues to affect ODC, it would theoretically be able to inhibit promotion. Using this assay, we performed a randomized Phase I study that determined that the dose of DFMO at 0.5 g/m²/day p.o. was safe and tolerable and was able to inhibit ODC in the skin for 10 months or more (88). This dose is also being used in Phase II studies in colon, bladder, and prostate cancers (89). Because many animal models are chem-

### Table 5  L-Pam-based adjuvant trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>B-05</td>
<td>L-Pam</td>
<td>0.15 mg/kg/day for 5 days for 17 courses</td>
<td>Improved DFS and OS in premenopausal women</td>
</tr>
<tr>
<td>B-07</td>
<td>L-Pam</td>
<td>0.15 mg/kg/day for 5 days for 17 courses</td>
<td>Improved DFS and OS in all subjects compared to surgery alone</td>
</tr>
<tr>
<td>FU</td>
<td>300 mg/m² i.v. for 5 days for 17 courses</td>
<td>Improved DFS and OS in all subjects compared to surgery alone: no evidence that three drugs are better than two</td>
<td></td>
</tr>
</tbody>
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*a Ref. 109.  
*b DFS, disease-free survival; OS, overall survival.*
Chemoprevention Strategies

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Vitamin C, fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phenols, flavones, aromatic isothiocyanates, diallyldisulﬁde, ellagic acid, antioxidants</td>
</tr>
<tr>
<td>Carcinogen formation, absorption</td>
<td>Aromatic isothiocyanates, glutathione, S2O3</td>
</tr>
<tr>
<td>Activation, DNA Damage, Mutagenesis</td>
<td>Beta-carotene, retinoids, tamoxifen, DHEA, terpenes, proteases and PG inhibitors, low fat diet, Calcium</td>
</tr>
<tr>
<td>Cell Proliferation, Promotion, Neoplasia</td>
<td></td>
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</tbody>
</table>

Fig. 3 Chemoprevention can interfere with carcinogen absorption and formation, activation, or DNA damage and promotion or progressions. Modified from Wattenberg (79).

ically induced, the question can be asked as to whether DFMO might be able to inhibit genetically derived tumors. Recently, Jacoby⁴ has reported that DFMO does reduce the number of intestinal tumors of mice with the min⁻¹ Apc abnormality. We have also proposed to test the activity of DFMO as a chemopreventive agent for skin cancers in normal adults, as well as in recipients of organ transplants.

Although the approaches to improving the outcomes of treatment are proceeding, increasingly inherent or induced drug resistance presents major barriers to effective therapies. Most cancers also occur in the population over 65 years of age, and the attempts at high-dose chemotherapy and stem cell replacement are fraught with danger. We need to explore new approaches that try to encourage cell differentiation, angiogenesis inhibition, and normal apoptosis. An alternative approach would be to investigate the strategy of controlling cancer by interfering with promotion or progression. Studies are already underway and have been shown to be effective in at least one clinical system (90). National trials are underway in prostate cancer (91) and breast cancer (85). Studies of chemoprevention offer another approach to controlling cancer. The mechanisms that seem to be important in preventing experimental cancers appear to be very general. This could open up the door to using a simple medication or supplement that will protect against several cancers.

References

R. Jacoby, personal communication.


Drug development in solid tumors: personal perspective of Dr. Emil J Freireich's contributions.

P P Carbone


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